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MATHEMATICAL MODELLING IN NEURAL ACTIVITIES

by

© DOUGLAS W. WILLIAMS

A THESIS

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ABSTRACT

This thesis is devoted to the study of mathematical models which have been proposed to describe the activities of the nerve cell. The models considered can be classified into two basic categories.

The models in the first category are those which describe the electrical behavior of the nerve membrane. Several mathematical model which describe the electrical behavior of the Loligo giant nerve axon membrane are considered. It will be shown that the models satisfy a generalized formulation. These models for nerve excitation, impulse initiation, are extended to incorporate the phenomena of impulse propagation in the nerve. One of the excitation models, that proposed by Hodgkin and Huxley (1952d), is modified to describe excitation and propagation in myelinated nerves. Finally two models are considered which account for the affect of the geometry of the dendrites on synaptic input.

The second category of mathematical models are those which describe the repetitive impulse activity of the nerve. Three such models are considered. As in the case of the excitation models these will be shown to be special cases of a generalized model. By analysing this general model it is possible to determine an interaction equation for the activity of nerves in a nerve network. This mathematical nerve network model forms the basis for three nerve network models which are considered. For one of these, the linear behavior of the solutions is examined for small nerve networks.

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TABLE OF CONTENTS

Page

ABSTRACT . . . . (iv)

ACKNOWLEDGEMENTS . . . . (v)

INTRODUCTION 1

I. MATHEMATICAL MODELS OF EXCITATION AND PROPAGATION IN THE NERVE

Introduction 3

§I.1 Early Mathematical Models for Nerve Excitation . . 6

§I.2 The Hodgkin-Huxley Theory for Nerve Excitation . . 13

§I.3 Alternative Formulations for the Hodgkin-Huxley Theory 23

§I.4 Physical and Chemical Models for Nerve Excitation 39

§I.5 Classification and Generalization of the Mathematical Models of Nerve Excitation 58

§I.6 Mathematical Models of Action Potential Propagation 72

§I.7 Mathematical Models of Excitation and Propagation in Myelinated Nerve 83

§I.8 Mathematical Models of the Significance of the Soma-Dendritic Region on the Nerve Excitability . 91

II. MATHEMATICAL MODELS OF IMPULSE PROCESSING IN THE NERVE

Introduction 105

§II.1 Random Walk Model of Neuronal Variability 107

§II.2 Exponential Decay Model of Neuronal Variability . 113

§II.3 Generalized Mathematical Model for Neuronal Variability 131

§II.4 Stationary Behavior of the Perfect Integrator and Leaky Integrator 143
§II.5 Mathematical Model of a Nerve Network 150
§II.6 Improved Nerve Network Models 159

SUMMARY 182

BIBLIOGRAPHY 185

INTRODUCTION

The purpose of this thesis is to survey the mathematical models which have been proposed to describe the activities of a single nerve cell.

The fundamental characteristic of the nerve cell is the nerve impulse. Functionally and morphologically the nerve itself can be divided into three parts; the axon, the soma, and the dendrites. A nerve impulse is generated in the axon portion of the nerve. The axon of one nerve impinges on the dendrites and soma of other nerves at points called synapses. Once an impulse has been generated in the axon, it will propagate over the entire axon and its effect will be transmitted to the soma-dendritic region of the other nerves through these synapses. The dendrites and soma of the nerve therefore act as a receptive field for stimulation of the nerve. In vitro, if sufficient stimulation is received in the soma-dendritic portion of the nerve, an impulse is generated in the axon portion.

The nerve impulse is essentially an electrical phenomena which can be recorded using microelectrodes. Furthermore, stimulation of the nerve by electrical current of a sufficient strength will initiate an impulse.

The physiological properties of the nerve originate in the membrane which forms its surface. Using the techniques of intracellular recording, extracellular recording and voltage-clamp it is possible to

determine the electrical properties of the nerve membrane. Chapter I of the thesis is devoted to a survey of mathematical models which have been formulated to generate this electrical behavior, in particular the initiation and propagation of a nerve impulse.

In certain cases the only information which can be obtained regarding the nerve is the pattern of impulses produced. Such impulse patterns show a great deal of variability in the interval between impulses. In Chapter II, mathematical models are considered which have been constructed to generate trains of impulses that resemble the experimentally observed nerve activity.

In studying the properties of the membrane and the impulse patterns, a wealth of experimental data has been assembled. The basic objectives of the mathematical formulations are to provide adequate theoretical concepts for the processes involved in the production of such behavior as well as methods for the analysis and comparison of this data. Using these derived formulations it is possible to predict the behavior of the proposed model, in this way providing a means of testing the model and establishing guidelines for further experimentation.

CHAPTER I

Introduction

In Chapter I the mathematical models which have been formulated to describe the electrical behavior of the nerve membrane are discussed. As stated in the Introduction, the initiation of the nerve impulse is associated essentially with the axon portion of the nerve. Since the impulse is an electrical phenomena, it is therefore necessary to consider the behavior of the axon membrane to electrical stimulation. The axon considered will be Loligo giant nerve axon which has been extensively studied.

In the absence of stimulation, there is a constant potential difference maintained across the membrane. If a stimulus in the form of a brief outward current pulse is applied to the nerve axon through a stimulating electrode touching the membrane, the recorded membrane potential changes from that of the resting potential. The magnitude of this change is dependent upon the amplitude of the applied stimulus. For a very weak stimulation, there is a temporary change of potential which decays away not only with time but also with distance from the electrode. With increasing stimulus strength the recorded potential change increases faster than the stimulus amplitude. The resulting potentials still decay both temporally and spacially. Finally a critical level of stimulus amplitude, called the threshold, is reached. If a stimulation, with this amplitude is administered to the axon, the recorded

potential curve increases abruptly to form an unmistakable triangular wave, the action potential, which does not decay with time and distance. For stimulus amplitudes above this level, which are not biologically damaging to the tissue, an action potential results. The action potential, a nerve impulse, is initiated near the electrode but immediately splits into two waves which travel at a constant waveform and velocity in opposite directions away from the electrode over the nerve. For natural stimulation through the soma-dendritic region, the action potential is a single wave which propagates over the entire nerve. Thus the action potential once initiated can be recorded at any point on the nerve as it passes. It is however, impossible to determine from such a recording where it has originated on the axon or the strength of the applied stimulus. Nerve excitation, the initiation of a nerve impulse, therefore is an all-or-none phenomena for which only the presence of absence without intermediates, can be deduced.

If a second above threshold stimulation is administered during a short time interval immediately following the action potential, it is possible to initiate another impulse. This time interval is called the absolute refractory period. Following this is a period of time during which an action potential can be initiated by the second stimulation but the threshold value in this case is above that for the resting nerve. During this relative refractory period the threshold level gradually returns to its resting state value.

If the first stimulus is below threshold for excitation, a nerve impulse is not produced, however, the membrane is affected. In a

short period following this subthreshold stimulation, the threshold value for a second stimulation will be lower than the resting value. After this phase, is a period of time during which the threshold for a second stimulus is greater than the resting value.

A stimulus applied to the nerve therefore has a dual effect. The first is excitatory, which results in a propagating nerve impulse if the stimulus is strong enough. Following this, the effect of the stimulus is to reduce the excitability of the nerve.

The mathematical models of nerve excitation are formulated in an effort to determine the variables and interconnections which result such electrical behavior. The major objective is to determine the construction and operation of the membrane. As shall be seen it has been possible in certain cases to associate with the mathematical model, a physical or chemical model of the membrane which satisfies the proposed mathematical description. Although the major objective has not been attained, the models have provided guidelines for physiological research, and have assisted in translating physiological concepts into quantitative and logical terms.

§I.1 Early Mathematical Models for Nerve Excitation

The first mathematical models were formulated in an attempt to explain the observed behavior of the nerve to an applied electrical stimulus. Experimentation made it possible to determine a number of quantitative relationships between the variables of the stimulus and the initiation of an action potential in the nerve. It was these relationships which provided the basis on which to test the models.

An early model which was extensively examined for its predictions regarding the strength-duration relationship in the nerve was proposed by Blair (1932). Blair postulated that the initiation of an action potential by an applied electrical current was governed by an "excitation process" in the nerve which was under the influence of the stimulus. The state of this process was assumed to approach a threshold level for excitation at a rate proportional to the applied voltage; and if the stimulus was removed before the threshold was reached, to decrease towards a resting level at a rate proportional to the state of the process. Thus the dynamic behavior of the state K of the "excitation process" satisfied

$$\frac{dK}{dt} = bV - kK \tag{I.1.1}$$

where V is the applied voltage, t is time, $K = 0$ is the resting

level, and both b and k are constants. An action potential was assumed to occur if

$$K \geq L \ . \tag{I.1.2}$$

The formulation given by (I.1.1) and (I.1.2) had originally been considered as a model for nerve excitation by Lapique (1907). The difficiency of the model was in its inaccurate formulation of the strength-duration relationship for a step current.

The solution of (I.1.1) for stimulation by a step current

$$V = \begin{cases} V_o, & t \geq 0 \\ 0, & t < 0 \end{cases}$$

is

$$K = \frac{bV_o}{k}\left(1 - e^{-kt}\right) \tag{I.1.3}$$

if the "excitation process" is at the resting level at $t = 0$. By setting $K = L$ in (I.1.3), the strength-duration relationship for a step current is given by

$$\log\left(\frac{V_o}{V_o - R}\right) = kt$$

where $R = \frac{kL}{V_o}$ is the rheobase voltage. The major difference between the computed graph of $\log\left(\frac{V_o}{V_o - R}\right)$ considered as a function of t for various values of k and the experimentally obtained graphs is that the curves in the latter case do not all pass through the origin. These

results suggested to Blair that the strength-duration relationship for a step current is of the form

$$\log\left(\frac{V_o}{V_o - R}\right) = kt + C$$

where C is a constant.

To theoretically justify the strength-duration relationship, Blair proposed the threshold L must be a function of V given by

$$L = \alpha \pm \beta V \tag{I.1.4}$$

where α and β are constants.

This revised formulation consisting of (I.1.1) and (I.1.4) permitted good approximations of the experimentally obtained strength-duration curves for stimulation by a step current, a linearly rising current with a sufficient rising rate, and condenser discharge (Blair: 1932-35). Unfortunately the theory was unable to account for a number of electrophysiological facts; in particular, the equations did not satisfy the constant quantity relationship for rectangular current of short duration (Hill: 1936b), and linearly rising current would always result in excitation irrespective of the gradient of the rise (Rashevsky: 1938). Furthermore, the assumption that the change of threshold depends only on the instantaneous voltage leads to conclusions which are contrary to known results (Rushton: 1934). These difficulties, Rushton suggested, result from the fact the theory does not adequately account for the accommodation property of the nerve.

The difficulties were overcome by a model proposed by Hill (1936a). For this model, that property of the nerve in the neighborhood of the stimulating electrodes which was influenced by the electric current was called the "local potential". The dynamic behavior of the "local potential" with only slight modification was the same as that of the state of the "excitation process" in Blair's formulation. The "local potential" K was determined by

$$\frac{dK}{dt} = bI - \frac{K - K_o}{k} \tag{I.1.5}$$

where I is the applied current, K_o is the resting level of the "local potential", and both b and k are constants. As in the model proposed by Blair, excitation was assumed to occur if the "local potential" reached the level L.

The major difference between the two theories was in the formulation for the behavior of the threshold to an applied electrical stimulus. Blair assumed the threshold was determined by (I.1.4) while Hill proposed that

$$\frac{dL}{dt} = \frac{K - K_o}{\beta} - \frac{L - L_o}{\lambda} \tag{I.1.6}$$

where β and λ are constant. The formulation given by (I.1.6) was adopted by Hill to account for accommodation in the nerve and the observation that the threshold gradually returned to a resting level L_o if the stimulus was removed. Hill simplified (I.1.6) by considering the particular case for which a nerve, described to be fully accommodated, responds as if no current were passing through it; that is,

$K - L = K_o - L_o$. Hence (I.1.6) reduces to

$$\frac{dL}{dt} = \frac{K - K_o}{\lambda} - \frac{L - L_o}{\lambda} . \tag{I.1.7}$$

Hill's model given by (I.1.5) and (I.1.7) was shown to be sufficient to explain anode break excitation, and the necessity of a minimum current gradient for excitation by a linear rising current (Hill: 1936a). The theory gave satisfactory descriptions of strength-duration curves for a variety of stimulating current, and good approximations of the results for numerous related experiments (Katz: 1939).

The theory of Hill has been classified as a "Two-Factor Theory" for nerve excitation. Hill's model is only one member of this class of models.

Rashevsky (1933) also proposed a two-factor theory to explain the initiation of an action potential by an applied electrical stimulus. The mathematical formulation for the theory was

$$\left\{ \begin{aligned} \frac{dK}{dt} &= bI - k(K-K_o) \\ \frac{dL}{dt} &= aI - m(L-L_o) \end{aligned} \right. \tag{I.1.8}$$

where I is the stimulating current, and a, b, k and m are constants. In this theory K was chosen to represent the concentration of an excitatory ion in the neighborhood of the stimulus while L represented the concentration of an inhibitory ion near the stimulus. K_o and L_o represented the resting level concentration of the respective ions.

Excitation was assumed to occur if $K \geq L$.

The formal difference between Hill's theory and Rashevsky's theory is that in the latter, the term which accounts for accommodation is a function of the applied current, while in the former the term is an implicit function of the applied stimulus.

In 1934, Monnier proposed a two-factor theory for excitation which depended on a single process, the "state of excitation". During the application of a constant current I , the "state of excitation" was defined by

$$\epsilon = KI(e^{-\frac{t}{\tau_1}} - e^{-\frac{t}{\tau_2}}) \tag{I.1.9}$$

where K, τ_2 , and τ_1 are constants. Hill (1936a) succeeded in showing that ϵ corresponded to the quantity $(L_o - K_o) - (L - K)$ of his theory, and that theoretical predictions regarding excitation for the two are equivalent.

The final model to be considered in this section is the generalized model of the "Two-Factor Theory" class proposed by Young (1937). The mathematical formulation was

$$\left\{\begin{aligned} \frac{dK}{dt} &= k_{11}(K - K_o) + k_{12}(L - L_o) + aI \\ \frac{dL}{dt} &= k_{21}(K - K_o) + k_{22}(L - L_o) + abI \end{aligned}\right. \tag{I.1.10}$$

where k_{11}, k_{12}, k_{21}, k_{22}, a and b are constants, K represents the excitatory process with resting level K_o , L represents the threshold

with resting level L_o , and I is the current strength. Young showed that, in terms of time-intensity relationships, Rashevsky's and Hill's theories were equivalent to this more general formulation.

Although the two factor theories were a satisfactory representation of events leading to excitation by an electrical stimulation, they were unable, except in one case which will be considered in §I.5, to describe events following the initiation of the impulse. A further drawback of these theories is the fact that no physical basis existed for the variables which were chosen only to represent biological phenomena that had been experimentally observed. To overcome these difficulties more extensive knowledge of the nerve was required. This necessitated the advancement of experimental techniques and equipment. The most important development was the "voltage-clamp" technique of studying the nerve. This advancement lead to the single most important development in modelling nerve excitation, which is the subject of §I.2.

§I.2 The Hodgkin-Huxley Theory for Nerve Excitation

The most significant development in describing nerve excitation and events associated with it, was obtained by Hodgkin and Huxley (1952 a-d), initially working with Katz (Hodgkin, Huxley and Katz: 1952).

Experimental results obtained by employing the "voltage-clamp" technique on the axon of the giant nerve fiber of "Loligo" indicated that a current flowing through the membrane of the axon could be separated into a capacitance and an ionic current. The ionic current consisted of three components: a potassium current I_K , a sodium current I_{Na} , and a "leakage" current I_ℓ which was carried by chloride and other physically unidentified ions.

Hodgkin and Huxley postulated the ionic current to be a result of the movement of the ions down their respective electrochemical potential gradients. Hence, the current resulting from each component could be defined in terms of the ease with which the component ions crossed the membrane, the permeability of the ions, and the difference between the membrane potential and the equilibrium potential for the ions. Since the instantaneous current-potential difference relationship for each component was found to be linear, the mathematical formulations describing the current densities of the components were

$$\begin{cases} I_K = g_K(E_M - E_K) \\ I_{Na} = g_{Na}(E_M - E_K) \\ I_\ell = g_\ell(E_M - E_\ell) \end{cases} \tag{I.2.1}$$

E_K and E_{Na} are the equilibrium potentials for potassium and sodium, respectively, and g_K and g_{Na} denote the conductance per unit area of membrane of the respective ions. E_ℓ is the membrane potential at which the "leakage current" is zero and g_ℓ denotes the conductance per unit area of membrane of the ions contributing to the "leakage current". The conductance term in each case is a measure of the permeability of the component ions.

For practical application (I.2.1) was transformed into

$$\begin{cases} I_K = g_K(V - V_K) \\ I_{Na} = g_{Na}(V - V_{Na}) \\ I_\ell = g_\ell(V - V_\ell) \end{cases} \tag{I.2.2}$$

where

$$\begin{cases} V = E_M - E_r \\ V_K = E_K - E_r \\ V_{Na} = E_{Na} - E_r \\ V_\ell = E_\ell - E_r \end{cases} \tag{I.2.3}$$

and E_r is the resting membrane potential.

Thus the total current density I per unit area of membrane is

$$I = C_M \frac{dV}{dt} + g_{Na}(V - V_{Na}) + g_K(V - V_K) + g_\ell(V - V_\ell) \tag{I.2.4}$$

where $C_M \frac{dV}{dt}$ accounts for the capacitance current with C_M the measurement of membrane capacitance per unit area, and t is time.

The experimental results indicated C_M, V_K, V_{Na}, V_ℓ and g_ℓ are constant but g_K and g_{Na} are functions of both time and membrane potential. From the data Hodgkin and Huxley determined that for a given membrane potential the experimental curve of $g_K = g_K(t)$ was best described by assuming potassium conductance was proportional to the fourth power of a variable n which itself obeyed a first order differential equation. Hence

$$\left\{ \begin{aligned} & g_K = \overline{g_K}\, n^4 \\ & \frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \end{aligned} \right. \tag{I.2.5}$$

where $\overline{g_K}$ is a constant which represents the maximum potassium conductance, and $0 \leq n \leq 1$. α_n and β_n are rate constants which were determined to be functions of the membrane potential for a fixed temperature and calcium concentration. In the case of sodium conductance it was proposed that the experimental curve of $g_{Na} = g_{Na}(t)$ for a fixed membrane potential could be described best by assuming that g_{Na} was a function of two variables m and h , both of which obeyed first

order differential equations. The proposed equation are

$$(I.2.6) \qquad \begin{cases} g_{Na} = \overline{g_{Na}}\, m^3 h \\ \dfrac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \\ \dfrac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \end{cases}$$

where $\overline{g_{Na}}$ is a constant representing the maximum conductance, $0 \leq m \leq 1$ and $0 \leq h \leq 1$. As in the case of potassium conductance, for a fixed temperature and calcium concentration, the rate constants α_m, β_m, α_h and β_h were found to be functions of the membrane potential.

The functional relationships between the rate constants, in both (I.2.5) and (I.2.6), and the membrane potential were empirically determined to fit the experimental data and at the same time conform as closely as possible to the equation derived by Goldman (1943) for the movement of charged particles in a constant field. The resulting functions were

$$(I.2.7) \qquad \alpha_n = \frac{0.1(V + 10)}{e^{\frac{V+10}{10}} - 1}$$

$$(I.2.8) \qquad \beta_n = 0.125e^{\frac{V}{80}}$$

$$(I.2.9) \qquad \alpha_m = \frac{0.1(V + 25)}{e^{\frac{V+25}{10}} - 1}$$

(I.2.10) $$\beta_m = 4e^{\frac{V}{18}}$$

(I.2.11) $$\alpha_h = 0.07e^{\frac{V}{20}}$$

(I.2.12) $$\beta_h = \frac{1}{e^{\frac{V+30}{10}} + 1} .$$

The reason for trying to conform to Goldman's equation which is of the form

$$j = C \cdot V \frac{ae^{-bV} - d}{e^{-bV} - 1}$$

where C, a, b, and d are constants, will become clearer in the discussion of the proposed mechanism for membrane permeability changes.

Thus the set of equations (I.2.4) - (I.2.12) makes it possible to determine the total membrane current I as a function of time and membrane potential. These equations are referred to in the literature as the "Hodgkin-Huxley equations".

Hodgkin and Huxley, in addition to deriving an empirical formulation determining the membrane current, suggested a possible physical model to describe the potassium and sodium conductance changes in terms of the mathematical formulation. Potassium permeability was hypothesized to be controlled by potassium specific charged particles in the membrane, the movement of which was determined by the membrane

potential. Each region of potassium permeability in the membrane contained four sites. If all the four sites in such a region were simultaneously occupied by a charged particle, potassium was allowed to move through the membrane at that region, otherwise the membrane remained impermeable to potassium. In terms of the mathematical formulation, n, potassium activation, represents the probability that a charged particle is at a site. The rate constant α_n denotes the rate of movement of the particles onto the sites while β_n represents the rate of particle movement away from the sites.

Sodium permeability was also assumed to be determined by sodium specific charged particles in the membrane. However, in contrast to the situation hypothesized for potassium conductance, there were two distinct types of particles, an activating particle and an inactivating particle, which acted independently of each other. The membrane became permeable to sodium in a certain region when three of the four sites contained in that region were simultaneously occupied by activating particles. The region became impermeable to sodium if at least one of the sites was occupied by an inactivating particle. In terms of the mathematical presentation, m, sodium activation, represents the probability an activating particle is at a site, and h, sodium inactivation, denotes the probability an inactivating particle is not occupying a site. α_m and β_h represent the rate of movement of the activating and inactivating particles, respectively, onto a site. β_m and α_h denote the rate of movement of the respective particles in the opposite direction.

From this model proposed for the mechanism of permeability changes it is evident the objective of trying to conform to Goldman's equation was an attempt to account for the variation of the rate constants with membrane potential in terms of the effect of the electric field on the movement of the charged particles.

The Hodgkin-Huxley equations do not account for the passive bahavior of the membrane to electrical stimulation. In the form (I.2.4) - (I.2.12), they represent a squid nerve axon with the experimentally induced condition of a uniform membrane potential over the entire axon length or a "space-clamped" axon. With this assumption, the total membrane current is zero except during stimulation. The equations have been extensively examined to test their ability to simulate the actions of the squid giant nerve axon under these conditions. Although the existence of a unique solution has been demonstrated (Cole, Antosiewicz, and Rabinowitz: 1955), a closed solution has not been obtained. Thus the behavior of the equations has been studied by numerical methods and computer simulations.

The original investigation of the validity of the equations was carried out by Hodgkin and Huxley (1952d). To determine the response of the membrane potential to an impulse stimulation administered at time $t = 0$, Hodgkin and Huxley solved the equations using the numerical method of Hartree (1932-3). The form, amplitude, and threshold of the calculated membrane action potential compared well with the experiment results. By linearizing the equations, the damped oscillatory

behavior of the membrane potential resulting from small amplitude constant current stimulation was reproduced. The equations also successfully predicted the form of subthreshold responses, anode break responses, the response to stimulation during a refractory period, and impedance changes during the action potential.

Under certain circumstances the predictions of the model are not in keeping with known electrophysiological results. The equations predict an indefinite train of impulses for stimulation by a rectangular wave current of strength above a critical level (Cole, Antosiewicz and Rabinowitz: 1955; FitzHugh and Antosiewicz: 1959). However, for a "space-clamped" squid nerve, stimulation by a rectangular wave current always results in at most a finite number of impulses (Hagiwara and Oomura: 1958). This represents a serious discrepancy between the predictions of the model and the behavior of the squid nerve. The model also does not satisfy the all-or-none property of the nerve. FitzHugh and Antosiewicz (1959) using a digital computer demonstrated the existence of a continuous gradation in response amplitude ranging from that of a subthreshold response to that of a full action potential. This particular difference between the computed and experimental results is not considered to be serious but rather the result of the digital computer not being programmed to account for the spontaneous fluctuations in the membrane potential (FitzHugh: 1969).

Further testing of the equation's ability to simulate the behavior of the squid nerve has required modification of the equations

in a manner prescribed by experimental results. Certain experiments indicate that the dependent variables of the Hodgkin-Huxley equations can be altered by variables not accounted for by the equations. By modifying the equations in the manner determined by the experiment, the predictions of the equations can be compared with the behavior of the nerve.

Frankenhaeuser and Hodgkin (1957) observed that the membrane potential varied with the extracellular calcium ion concentration. The relationship between the change in membrane potential ΔV and the calcium concentration $[Ca]$ was experimentally determined to be

$$V = - 9.32 \ln \frac{[Ca]}{[Ca]_n}$$

where $[Ca]_n$ is the normal calcium concentration. Huxley (1959) incorporated this in equations (I.2.4) - (I.2.12) by substituting $V + \Delta V$ for V. The predictions of these modified equations agreed well with the experimental results for different calcium concentrations.

By injecting tetraethylammonium chloride into the squid nerve axon, an above threshold stimulation produces a long lasting action potential (Tasaki and Hagiwara: 1957). FitzHugh (1960) was able to reproduce this phenomena with the equations by reducing α_n and β_n by a factor of 100 and increasing α_h and β_h by a factor of 3. These modifications are supported in part by the voltage-clamp data which revealed that during the first few milliseconds of the response of a nerve injected with tetraethylammonium, the potassium current is

either absent or significantly delayed.

Calculations using these modifications agree with other experimental results also obtained from a nerve treated with tetraethylammonium. These include the abolition of the response to a repolarizing current of a critical threshold value applied during the plateau phase of the response, and the response to a second stimulation following the long lasting action potential. The impedance changes occurring during the plateau, however, are not reproduced by the equations.

Another validation of the equations using an analogous approach has been carried out to predict the effect of high extracellular potassium concentration on the squid nerve axon (George and Johnson: 1961). In this case only partial success was obtained in reproducing the behavior of the nerve.

The Hodgkin-Huxley theory, with certain exceptions, has demonstrated a remarkable ability to simulate the behavior of the "space clamped" squid axon to electrical stimulation. However, Hodgkin and Huxley (1952d) expressed two important reservations regarding the formulation. First, the equations have been empirically determined and as such may not be the only satisfactory formulation. Second, the success of these equations does not necessarily provide a proof that the hypothesized mechanism for membrane permeability changes is valid. It is in the light of these two remarks that alternative formulations and interpretations of the Hodgkin-Huxley theory have arisen. These alternative formulations will be discussed in §I.3.

§I.3 Alternative Formulations for the Hodgkin-Huxley Theory

The reservations regarding the Hodgkin-Huxley formulation expressed in the last paragraph of §I.2 have fostered two avenues of research. Investigations have been initiated to determine alternative chemical and physical mechanisms for membrane permeability changes which satisfy the Hodgkin-Huxley equations, and alternative empirical formulation which satisfy the experimental data obtained by Hodgkin and Huxley (1952d). Although the success of the equations does not establish conclusively the validity of the hypothesized mechanism of permeability changes, it does lend support. Other physical and chemical mechanisms which satisfy the equations therefore must also be considered in the realm of possibilities. These hypothetical mechanisms serve to provide a guide line for future experimental work to determine the actual mechanism. Alternative mathematical models which satisfy the experimental results could also suggest different physical or chemical mechanisms for the membrane permeability changes. In these cases the mathematical formulations are available to distinguish between the mechanisms. With the mathematical formulations it is possible to predict the behavior of the squid nerve axon thereby providing a quantitative means to distinguish the models and establish to a certain degree the validity of each permeability mechanism. In §I.3, certain of the alternative empirical formulations and mechanisms for the permeability changes which have been derived, will be described.

In 1963, Agin derived an alternative theoretical basis for the conductance equations (I.2.5) - (I.2.12) of the Hodgkin-Huxley model, thereby providing an alternative physical framework on which to formulate the mechanism for membrane permeability.

The motivation for the model was the form of the equation for the rate constant α_n resulting from a transformation. By defining

$$Q_j = j\left(\frac{V + a}{a}\right), \quad a = 10 \tag{I.3.1}$$

then α_n given by (I.2.7) can be transformed to

$$\alpha_n = \frac{\frac{1}{a}\sum_{j=0}^{\infty} Q_j e^{-Q_j}}{\sum_{j=0}^{\infty} e^{-Q_j}} . \tag{I.3.2}$$

In this form α_n is proportional to the mean value function of statistical mechanics. Further developments result from considering the solution of the potassium conductance equation (I.2.5) for a given constant membrane potential and initial condition

$$n_o = n\Big|_{t=0} = \frac{\alpha_n - 1}{\alpha_n + \beta_n} . \tag{I.3.3}$$

The solution is

$$g_K = \overline{g_K}\left(\frac{\alpha_n - e^{-(\alpha_n+\beta_n)t}}{\alpha_n + \beta_n}\right) . \tag{I.3.4}$$

By writing $\beta_n = be^{\frac{bV}{a}}$, where $b = \frac{1}{8}$, and employing (I.3.2), the initial condition (I.3.3) can be reformulated as

$$n_o = \frac{\sum_{j=0}^{\infty} (Q_j - a)e^{-Q_j}}{\sum_{j=0}^{\infty} (Q_j + abe^{\frac{bV}{a}})e^{-Q_j}} . \tag{I.3.5}$$

Moreover, the steady state value of n , given by

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} , \tag{I.3.6}$$

is equivalently written as

$$n_\infty = \frac{\sum_{j=0}^{\infty} Q_j e^{-Q_j}}{\sum_{j=0}^{\infty} (Q_j + abe^{\frac{bV}{a}})e^{-Q_j}} . \tag{I.3.7}$$

In forms (I.3.5) and (I.3.7), n_o and n_∞ represent statistical distribution functions with properties identical to equilibrium distribution functions of statistical mechanics. Similar formulations can be obtained for the rate constants α_m and β_m , and initial and steady state values of m . Furthermore the rate constant β_h of sodium inactivation given by (I.2.12) is analogous to the Fermi-Dirac distribution function.

This analysis suggested that a possible theoretical framework on which to base the empirical conductance equations could be obtained

using statistical mechanics. To illustrate this hypothesis, Agin, using an abstract model satisfying appropriate probabilistic constraints derived an equation which is formally equivalent to the potassium conductance equation (I.3.4). Although the analysis was not carried out, it was suggested that in an analogous manner a model could also be derived which would produce equations formally equivalent to the sodium conductance equations.

The analysis of Agin suggests a possible framework for a physical model of membrane permeability, the mathematical description of which is the Hodgkin-Huxley equations. The original Hodgkin-Huxley formulation remained unchanged. An alternative form of the potassium conductance equation (I.2.5) was derived by Cole and Moore (1960). It was found necessary to modify these equations in order to account for a time delay in the potassium current I_K, resulting from the depolarization of a prehyperpolarized squid axon. The required reformulation is

$$g_K = \overline{g_K}\, n^{25} \tag{I.3.8}$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n \tag{I.3.9}$$

where $\overline{g_K}$ is a constant, and both α_n and β_n are functions of the membrane potential. With the appropriate values of α_n, β_n and initial condition for (I.3.9), the reformulation proved adequate in representing g_K for the experimental conditions originally considered by Hodgkin and Huxley (Cole and Moore: 1960). The model thereby extends the range

of membrane potentials over which the equations accurately simulated the behavior of the squid axon.

A satisfactory alternative formulation for both the potassium and sodium conductance equations of the Hodgkin-Huxley model was proposed by Hoyt (1963).

In the presentation by Hoyt, potassium conductance g_K was assumed to be a function of the variable ν_K , which obeys the first order differential equation

$$\frac{d\nu_K}{dt} = a_K(\nu_{K\infty} - \nu_K) \tag{I.3.10}$$

where $\nu_{K\infty}$ and a_K are functions of the membrane potential. The functions

$$g_K = g_K(\nu_K)$$

$$\nu_{K\infty} = \nu_{K\infty}(V)$$

and

$$a_K = a_K(V)$$

where V , as in the Hodgkin-Huxley formulation denotes the difference between the membrane potential and resting potential, were empirically determined in order that for a given membrane potential, the graph of $g_K = g_K(t)$ agreed with the experimental results obtained by Hodgkin and Huxley (1952d).

Sodium conductance g_{Na} was defined to be a function of the single variable ν_{Na} which satisfies the second order differential

equation

$$\text{(I.3.11)} \qquad \frac{d^2\nu_{Na}}{dt^2} + \frac{\gamma d\nu_{Na}}{dt} + \delta[\nu_{Na} - \nu_{Na\infty}] = 0$$

where $\nu_{Na\infty}$, γ and δ are functions of the membrane potential. As in the case of potassium conductance, the functions

$$g_{Na} = g_{Na}(\nu_{Na})$$

$$\nu_{Na\infty} = \nu_{Na\infty}(V)$$

$$\gamma = \gamma(V)$$

$$\delta = \delta(V)$$

and the initial condition

$$\left.\frac{d\nu_{Na}(t,V)}{dt}\right|_{t=0} = 0$$

were chosen to obtain the best fit of the curve $g_{Na} = g_{Na}(t)$, for a given membrane potential, to the results of Hodgkin and Huxley (1952d).

In order to simplify the analysis, Hoyt proposed that equation (I.3.11) results from the system of coupled first order differential equations

$$\text{(I.3.12)} \qquad \begin{cases} \dfrac{du_{Na}}{dt} = - k_1 u_{Na} + k_2 \\[2ex] \dfrac{d\nu_{Na}}{dt} = k_1 u_{Na} - k_3 \nu_{Na} + k_4 \end{cases}$$

where k_i for $i = 1,2,3,4$ are functions of the membrane potential. This system of equations is equivalent to the second order differential equation

$$(I.3.13)\qquad \frac{d^2\nu_{Na}}{dt^2} + (k_1 + k_3)\frac{d\nu_{Na}}{dt} + k_1k_3\left(\nu_{Na} - \frac{k_2 + k_4}{k_3}\right) =$$

$$= \left(\nu_{Na}\frac{dk_1}{dV} - \nu_{Na}\frac{dk_3}{dV} - \frac{dk_4}{dV}\right)\frac{dV}{dt}\ .$$

For a constant membrane potential, equation (I.3.13) reduces to the form of (I.3.11) and the functions $k_i = k_i(V)$ for $i = 1,2,3,4$ can be determined by comparing coefficients.

The validity of Hoyt's formulation was examined by computing the form of a membrane action potential. Comparison of the result with that computed by Hodgkin and Huxley (1952d) revealed a difference only during the repolarization phase.

Hoyt also proposed a possible physical mechanism for the membrane permeability changes, which would satisfy the mathematical formulation. In the case of potassium,the membrane was assumed to possess potassium specific pores,each of which contains a series of p dipoles. Each dipole possesses two stable orientations, of which only one allows the potassium ion to pass through the membrane. A quantitative description of the mechanism for permeability changes was obtained by assuming the two stable orientations to be separated by an energy barrier ϵ . ϵ would therefore correspond to the energy required to orient a dipole to permit the passage of a potassium ion, and a pore with $j(j = 0,1,2,...,p)$ dipoles oriented to permit the passage of potassium could be considered to possess the amount of energy $j\epsilon$. With this formulation a pore resembles a quantum system with a ground

state, corresponding to the case in which all dipoles are oriented to prevent the passage of potassium, and p excited states each determined by the number of dipoles oriented to allow the passage of potassium ions.

A collection of such pores obey Boltzmann statistics in which case the probability P_p , that a pore has all dipoles in a potassium permeable orientation and the pore is open, is given by

$$P_p = \frac{e^{-\frac{p\epsilon}{kT}}}{\sum_{j=0}^{p} e^{-\frac{j\epsilon}{kT}}} \tag{I.3.14}$$

or equivalently

$$P_p = \frac{e^{-\frac{p\epsilon}{kT}}\left(1 - e^{-\frac{\epsilon}{kT}}\right)}{1 - e^{-\frac{(p+1)\epsilon}{kT}}} \tag{I.3.15}$$

where k is Boltzmann's constant and T is the absolute temperature. Further, the probability y that in equilibrium a dipole is oriented to allow potassium to pass is

$$y = \frac{e^{-\frac{\epsilon}{kT}}}{1 + e^{-\frac{\epsilon}{kT}}} . \tag{I.3.16}$$

Substitution of (I.3.16) into (I.3.15) yields

$$P_p = \frac{1 - 2y}{y\{(\frac{1-y}{y})^{p+1} - 1\}} . \tag{I.3.17}$$

By comparing the graphs of $g_K = g_K(\nu_K)$ and $P_p = P_p(y)$, Hoyt determined potassium conductance g_K as a function of the probability $P_p(y)$ that a pore is open. Agreement between the two functions was attained with $p = 9$ and the linear transformation $y = 0.357 + 0.00394\nu_K$. The formulation for g_K defined as a function of $P_p(y)$ is

(I.3.18) $$g_K = g_o N P_9(y)$$

where g_o denotes the conductance of a pore with all dipoles oriented to permit the passage of potassium and N is the number of pores per unit area of membrane. This formulation enables the determination of the range of ν_K, thereby providing the means to approximate the delay of the potassium current I_K, resulting when a depolarizing voltage-clamp is preceeded by a large hyperpolarization. The calculated delay was in close agreement with that determined by Cole and Moore (1960).

Hoyt's hypothesized physical model for the potassium permeability mechanism presents one complication. The difficulty lies in the fact that for large changes of ν_K the calculated energy barrier ϵ between the two orientations is too large to permit the proposed serial arrangement of the dipoles.

The sodium permeability changes, Hoyt suggested,could be modeled in a similar manner except in this case the dipoles would possess three stable orientations only one of which would allow a sodium ion to pass.

A feature common to the models proposed by Hodgkin and Huxley, and by Hoyt is that potassium conductance at each permeability region or pore is governed by a number of identical events which occur independently of each other. If the potassium conductance equations derived by Cole and Moore are interpreted in the same manner as those of Hodgkin and Huxley, then twenty-five identical events must occur at each potassium specific region in order for the membrane to become permeable. Tille (1965) suggested that it is difficult to reconcile the fact that these events occur independently of each other and at the same time are localized within a region or near a pore in such a manner that the action of any one can prevent the passage of a potassium ion.

Johnson and Tille (unpublished) determined that the experimental data of Hodgkin and Huxley (1952d) for potassium conductance considered as a function of time for a given membrane potential can be empirically described by

$$g_K = \overline{g_K}\, n \tag{I.3.19}$$

$$\frac{dn}{dt} = kn(\omega - n)^2 - \beta n \tag{I.3.20}$$

where k and $\overline{g_K}$ are constants, and both ω and β are functions of the membrane potential. Equation (I.3.20) lends itself to the physical interpretation of describing a system of dipoles each of which can exist in one of two stable orientations but which can change orientation only if an adjacent dipole is in a specific orientation.

This analysis of Johnson and Tille laid the foundation for a mathematical model of potassium conductance, proposed by Tille (1965), which would avoid the above mentioned difficulty of the previously described models. The model avoids the complication by requiring only a single event, the reorientation of a dipole or the movement of a blocking particle to open or close a potassium specific pore. One restriction to this simplified model was however required; that is, a pore could change state only if an adjacent pore is open.

In the mathematical formulation of the model, potassium conductance g_K was defined to be

$$g_K = \overline{g_K}\,\eta \tag{I.3.21}$$

where $\overline{g_K}$ is a constant and η denotes the probability a given pore is open. By assuming the pores to be distributed over the axon in a square array then

$$\frac{d\eta}{dt} = \alpha\eta(1-\eta)(4-6\eta+4\eta^2-\eta^3) - \beta\eta(4-6\eta+4\eta^2-\eta^3) \tag{I.3.22}$$

where $\eta(1-\eta)(4-6\eta+4\eta^2-\eta^3)$ is the probability a pore is closed and at least one adjacent pore is open, and $\eta^2(4-6\eta+4\eta^2-\eta^3)$ is the probability a pore is open and at least one adjacent pore is open. α and β denote the rates of departure and arrival of the blocking particles, respectively. These rate coefficients were assumed to be functions of the membrane potential and were empirically determined to be

$$\text{(I.3.23)} \qquad \begin{cases} \alpha(V) = \dfrac{0.0079(V - 5.9)}{1 - e^{\frac{5.9-V}{4.0}}} \\ \\ \beta(V) = 0.79e^{-\frac{V}{54}} . \end{cases}$$

Rearrangement of (I.3.22) reveals that it is of a form closely resembling (I.3.20).

Computations carried out using (I.3.21), (I.3.22) and (I.3.23) for the potassium conductance equations in the Hodgkin-Huxley formulation gave good approximations of the experimental results obtained by Hodgkin and Huxley (1952d) and by Cole and Moore (1960).

Another model for the mechanism of potassium permeability changes which avoids the difficulty of prescribing the precise number of events occurring at a region or pore was described by FitzHugh (1965). This model assumed that associated with each pore is an infinite number of sites. If at least one of the sites is occupied by a potassium specific charged particle, the potassium ion is prevented from moving through the membrane.

Potassium conductance g_K , as in Tille's formulation, was defined to be

$$\text{(I.3.24)} \qquad g_K = \overline{g_K}\,\eta$$

where $\overline{g_K}$ is a constant and η is the probability a pore is open. To obtain the dynamic behavior of the system, it was supposed the charged

particles enter and leave the sites at random, independently of the number of sites occupied. Further, the rate of arrival and departure of the particles is governed by the rate constants α and β, respectively, both of which were assumed to be functions of the membrane potential. With these assumptions, the probability x_j that a given pore has j sites occupied is

$$\text{(I.3.25)} \qquad \frac{dx_j}{dt} = \alpha x_{j-1} - (\alpha + j\beta)x_j + (j+1)\beta x_{j+1} \; ;$$

$$\text{for } j = 0,1,2,\ldots \text{ and } x_{-1} = 0 \, .$$

The steady state solution of (I.3.25) for a given membrane potential is

$$\text{(I.3.26)} \qquad x_j = \frac{(\frac{\alpha}{\beta})^j x_o}{j!} \quad \text{for } j = 0,1,2,\ldots \, .$$

Since $\sum_{j=0}^{\infty} x_j = 1$ then $\eta \equiv x_o$, the probability a pore is open, is $e^{-\frac{\alpha}{\beta}}$ and equation (I.3.26) can be explicitly written as

$$\text{(I.3.27)} \qquad x_j = \frac{(\frac{\alpha}{\beta})^j e^{-\frac{\alpha}{\beta}}}{j!} \quad \text{for } j = 0,1,2,\ldots \, .$$

By (I.3.27), for a given membrane potential the number of occupied sites for a given pore in a steady state obeys a Poisson distribution with mean $\frac{\alpha}{\beta}$. Assuming the number of occupied sites for a given pore also obeys a Poisson distribution during the transient state, that is assuming the solution for a step current applied at $t = 0$ to be $x_j = \frac{(\mu)^j e^{-\mu}}{j!}$ transforms (I.3.25) to

$$\frac{d\mu}{dt} = \alpha - \beta\mu; \quad \text{for each} \quad j = 0,1,2,\ldots \tag{I.3.28}$$

Therefore, since the derivation of (I.3.28) is independent of the functional dependence of α and β on membrane potential and time, the dynamic behavior of η is given by

$$\eta = e^{-\mu} \tag{I.3.29}$$

where μ satisfies (I.3.28). To determine the functions $\alpha = \alpha(V)$ and $\beta = \beta(V)$, FitzHugh assumed for convenience that these obeyed the Eyring theory of reaction rates. The functional dependence of α and β one the membrane potential was therefore given by

$$\left\{\begin{aligned} \alpha(V) &= A\, e^{\left[-\frac{H + \frac{C+rNV}{2}}{25}\right]} \\ \beta(V) &= B\, e^{\left[-\frac{H - \frac{C+rNV}{2}}{25}\right]} \end{aligned}\right. \tag{I.3.30}$$

A, B , and C are constants, H denotes the energy barrier which the particles must cross to enter or leave a site, r is the fraction of the total membrane potential between the two wells, and N is the number of electronic charges on the particle.

FitzHugh's formulation for potassium conductance is therefore given by (I.3.24), (I.3.28), (I.3.29), and (I.3.30). With empirically determined values of α and β and the appropriate initial condition for (I.3.28), the solution of the conductance equations fitted the

experimental results of both Hodgkin and Huxley (1952d), and Cole and Moore (1960) with reasonable accuracy.

The basic model can also be generalized to include the case in which more than one species of charged particles controls the permeability of the ion, as is the case hypothesized for sodium permeability in the Hodgkin-Huxley model. For the general model, the pore was assumed to be closed if at least one particle, irrespective of which type, occupied a site. The formulation was derived by modifying (I.3.29) and (I.3.30) to

(I.3.31) $$\eta = e^{-\sum_{i=1}^{p} \mu_i}$$

and

(I.3.32) $$\frac{d\mu_i}{dt} = \alpha_i - \beta_i\mu_i; \qquad i = 1,2,\ldots,p$$

respectively, where p is the number of distinct species of charged particles, and α_i and β_i represent the rate of movements of the particles of the i^{th} species.

An interesting feature of the model proposed by FitzHugh is that by assuming the number of sites associated with each pore to be finite reduces the formulation for potassium permeability to that of the Hodgkin and Huxley model or Cole and Moore model. This results from the fact that with a finite number of sites, the Poisson distribution is replaced by a binomial distribution in which case (I.3.29) and (I.3.28) would be replaced by

(I.3.33) $$\eta = x_o = (1 - \frac{\mu}{S})^S$$

and

(I.3.34) $$\frac{d\mu}{dt} = \alpha - (\frac{\alpha}{S} + \beta)\mu$$

where S denotes the number of sites at each pore. For $(1 - \frac{\mu}{S}) = n$, $S = 4$, and the appropriate definition of α and β, equations (I.3.24) (I.3.33), and (I.3.34) give the original formulation for potassium conductance proposed by Hodgkin and Huxley. With $S = 25$ the equations are formally equivalent to the model of Cole and Moore.

A number of different models have been discussed in §I.3 and in each case certain aspects of the behavior of the squid nerve axon is accurately simulated by the models. There do, however, exist certain similarities between the models. In particular, the mathematical structure of the equations for certain of the models are similar in their formulation for certain qualitative features of the axon necessary for excitation. These structural similarities permit the classification and comparison of the models. Before considering such a classification of the models it is desirable to extend the variety of excitation models considered. A class of models which are formulated in a different manner from those discussed to this point will be described in §I.4.

§I.4 Physical and Chemical Models for Nerve Excitation

For the mathematical models of nerve excitation considered in §I.2 and §I.3, the equations were empirically determined then a physical mechanism, which satisfies the mathematical formulation, was porposed to explain the membrane permeability changes. A number of mathematical models for excitation have been derived by postulating the mechanism of permeability changes the then deriving the equations. In each case, the meahcnism was based on certain physiological or histological features of the squid axon which are conceivably related to such permeability changes. The mathematics was then employed to describe the model and make predictions regarding it. In §I.4 three models which were constructed in this manner will be considered.

Mullins (1959) proposed that the ionic currents result from the movement of ions through membrane pores. In contrast to previously discussed pore models, it was supposed that the pores are not ion specific. Ionic selectivity of the membrane was accounted for by assuming membrane pores discriminate between ions on the basis of ion size. For the model, a permeable ion is permitted to pass through a pore only if the ion and pore have identical radii.

The membrane permeability changes were attributed to changes in the distribution of the pore sizes. At zero membrane potential, the pore sizes were hypothesized to be distributed with a Gaussian distribution such that the mode of the distribution corresponds to the radius

of the potassium ion. Reduction of the membrane potential to that of the resting membrane potential results in the continuous transformation of the distribution of pore sizes present at the zero membrane potential to a Gaussian distribution with mode that of the radius of a sodium ion at the resting membrane potential. This change of the distribution of pore sizes with membrane potential was assumed to follow from the deformation of the membrane by nonpermeable ions and ions of low permeability. Such ions are forced into the entrances of certain pores by the non-zero membrane potential, thereby altering the size of the pore to that of the intruding ions. The ions considered to be responsible for this action are calcium ions at the extracellular membrane surface and isethionate ions at the intracellular surface. In both case, the ionic radii are equivalent to that of the sodium ion and at the resting membrane potential these ions are assumed to block all pores of that radius. Subsequent depolarization of the membrane removes the intruding ions from a blocked pore and restores the pore to its undistorted size.

The axon membrane under the influence of an electrical field exhibits the properties of a parallel plate condenser. In this case the mechanical force exerted by the calcium or isethionate ion is proportional to the square of the membrane potential. Since this applied force results in the redistribution of pore sizes, Mullins proposed that the mode $\overline{r}$ of the distribution of pore sizes is a linear function of the square of the membrane potential given by

$$\overline{r} = r_K - kE_M^2; \qquad (\overline{r} > r_{Na}) \tag{I.4.1}$$

where r_K and r_{Na} are the radii of the potassium and sodium ion, respectively, and k is a constant. With (I.4.1), the probability h_o that the extracellular entrance to a pore is of the sodium ion radius at a given membrane potential is given by the error function

$$h_o = \int_{r=r_{Na}-\delta}^{r=r_{Na}+\delta} ce^{-(\bar{r}-r)^2} dr \tag{I.4.2}$$

where δ is an arbitrarily chosen tolerance and c is a constant. A similar formulation can be written for h_i , the probability the intracellular entrance of a pore is of the sodium ion radius. By assuming that in the steady state all sodium sized pores are blocked at both entrances, Mullins succeeded in deriving expressions for both potassium and sodium conductance in terms of h_o and h_i .

For this physical model proposed for ion permeability and membrane permeability changes, potassium conductance g_K is defined to be

$$g_K = \overline{g_K}\, j_o j_i \tag{I.4.3}$$

where j_o and j_i are the probabilities that extracellular and intracellular entrances, respectively, of a pore have the radii of the potassium ion, and $\overline{g_K}$ is a constant. Calculations indicated that the results of this formulation were comparable if j_o and j_i are replaced by $b + (1-h_o)$ and $b + (1-h_i)$, where b denotes the probability that the entrance of a pore is of the potassium ion size in a fully distorted membrane. The formulation for potassium conductance was therefore given

by

$$g_K = \overline{g_K}\,[b + (1 - h_o)][b + (1 - h_i)] \ . \qquad \text{(I.4.4)}$$

The expression for sodium conductance g_{Na} is more complex than that for potassium since it is necessary to account for the competition between sodium and the blocking ions, and the inactivation of the sodium current. In the model, the blocking ions were assumed to be embedded in the pore entrance in a partially hydrated form. Removal of such an ion from the pore requires energy to completely hydrate the ion. The effect of this energy barrier at the extracellular surfaces was incorporated in the formulation by supposing that upon instantaneous depolarization, the distribution of entrances which remain blocked is an exponential distribution with mean k_o . At the intracellular surface the distribution is exponential with mean k_i . Inactivation of the sodium current was assumed to be the property of the membrane itself. Once the intruding ion is removed from the entrance, the internal structure of the membrane restores the pore to its undistorted size. Hence sodium permeability is prevented if the undistorted size of the unblocked pore is not that of the sodium ion. Mathematically sodium inactivation was expressed in terms of the distribution of pores which have been unblocked by depolarization and have returned to their undistorted size. The distribution was chosen to be an exponential with mean k_h .

Thus for sodium permeability to occur, a pore of sodium ion radius must become unblocked and a sodium ion must penetrate the pore

before it attains a size outside the limits which permit the passage of this ion. The equation chosen to describe the probability the entrance to a pore is both unblocked and of the sodium ion size was that for the concentration of an intermediate in a series of chemical reactions. Sodium conductance g_{Na} was therefore given by

$$\text{(I.4.5)} \qquad g_{Na} = \overline{g_{Na}} \left[\Delta h_o \left(\frac{k_o}{k_h - k_o} \right) \left(e^{-k_o t} - e^{-k_h t} \right) \right] \left[\Delta h_i \left(\frac{k_i}{k_h - k_i} \right) \left(e^{-k_i t} - e^{-k_h t} \right) \right]$$

where $\overline{g_{Na}}$ is a constant, t denotes time, and Δh_o and Δh_i represent the probabilities an extracellular and intracellular entrance, respectively, is open during the depolarization. The quantities in square brackets of (I.4.5) represent the probabilities an entrance is both unblocked and of the sodium ion size.

The mathematical description for the electrical behavior of the squid axon proposed by Mullins consists of (I.2.3) - (I.2.5) of the Hodgkin-Huxley equations together with (I.4.1) - (I.4.5). Although extensive analysis of this formulation has not been carried out it has been demonstrated that the formulation for potassium conductance considered as a function of membrane potential yields accurate results (Mullins, 1959).

For Mullin's theory, the structure of the membrane was significant only in the inactivation of the sodium current. To incorporate this membrane phenomena in the theory it was not necessary to provide a

description of the membrane structure. A model for nerve excitation which requires the explicit description of the structure of the membrane was proposed by Goldman (1964). The model was based on the electron microscope evidence which indicated the axon membrane consists of a bimolecular layer of lipid covered on either side by a protein layer. At intervals throughout the bilayer, phospholipids are also found to be present. Each phospholipid consists of a polar phosphate end group, which is situated at the surface of the membrane, and a hydrocarbon chain, which extends into the interior of the membrane. A polar end group which is not bonded to a membrane protein forms a dipole which can bind to ions in the external medium. This fact forms the cornerstone of Goldman's theory for cationic permeability. In order for a cation to penetrate the membrane it must initially be bonded to such a dipole. Permeability is initiated by the collision of an unbonded cation with the bonded cation with sufficient energy to break the bond and drive the released cation into the membrane. The released cation then diffuses through the membrane interior which is assumed to be a continuous, inert medium.

To account for the ionic specificity of the membrane, Goldman proposed that an unbonded phosphate group, which can change configuration with the alteration of the electric field and ionic environment present, would in this manner change its combining properties for different ions. For each phospholipid, three interchangeable ion specific configurations of the phosphate end group were considered. These are denoted by C_I, C_{II}, and C_{III}. Under the influence of the electric field for the

resting membrane potential, configuration C_I, which favors the bonding of calcium ions, predominates. Removal of this electric field by depolarization results in a predominance of dipoles in configuration C_{II}, for which the phosphate group has an affinite for sodium ions. Also present in a significant proportion during depolarization of the membrane is the potassium specific configuration C_{III}. By considering the interchange between C_{II} and C_{III} to be independent of the electric field present, Goldman proposed that during depolarization sodium permeability would attain a maximum then decline and be replaced by potassium permeability.

If it is assumed the ionic exchange at the polar end group occurs with sufficient rapidity that the configurational changes represent the rate-limiting steps it is possible to quantitatively describe the ionic currents resulting at the membrane surface in terms of the end groups and configurational changes. For convenience in determining the mathematical formulation only phosphate end groups at the extracellular surface membrane were assumed to participate in the membrane transfer of cations. To obtain the quantitative description, Goldman considered the total number n_T of end groups per unit area of extracellular membrane surface which are in the form of dipoles. Of this total n_I, n_{II}, and n_{III} denote the number with configuration C_I, C_{II}, and C_{III}, respectively. The ionic currents were defined in terms of these variables and their dynamic behavior which is dependent upon the interchange of the configurations and the effect of the ionic environment present.

The rates of interchange among the configurations are governed by the rate constants k_1, k_2, k_3, k_4, k_5, and k_6. Rate constants k_1 and k_5 denote the rate of change from C_I into C_{II} and C_{III}, respectively. k_2 and k_6 represent the respective reverse transformation rates. k_3 denotes the rate of change of end groups from configuration C_{II} into C_{III}, while k_4 denotes the rate of change in the opposite direction. Since k_1, k_2, k_5 and k_6 are dependent on the electric field strength, it is possible to derive explicit expressions for these in terms of the energy required to change the configuration. The formulations are

$$\text{(I.4.6)} \qquad \left\{ \begin{aligned} k_1 &= m_1 e^{\gamma\theta_s} \\ k_2 &= m_2 e^{-\gamma\theta_s} \\ k_5 &= m_5 e^{-\gamma\theta_s} \\ k_6 &= m_6 e^{\gamma\theta_s} \end{aligned} \right.$$

where $e^{\gamma\theta_s}$ and $e^{-\gamma\theta_s}$ are expressions which account for the energy required to change the configuration, θ_s is the potential across the surface of the membrane, and m_1, m_2, m_5 and m_6 are constants.

The effect of the ionic environment present is to restrict the number of phosphate end groups which are available for configurational changes. In particular, end groups with configuration C_I or C_{III} which are bonded to their preferred cations can not participate in configurational changes. In order to determine the number of end groups which are bonded to cations, it is necessary to take into account the

velocity and concentration of unbonded cations and the number of available end groups. For those phosphate end groups which are in configuration C_I , the number n_{Ca} per unit area of membrane which are bonded to calcium is given by

(I.4.7)
$$n_{Ca} = p\,[Ca]_e n'_I$$

where $[Ca]_e$ is the concentration of calcium in the extracellular medium, p is a constant representing the velocity of ions, and n'_I is the number of end groups with configuration C_I which are not bonded to a calcium ion. The corresponding formulation for end groups in configuration C_{III} is more complex since potassium ions are present in the interior of the membrane as well as the extracellular medium, which is not the case for calcium. The number n_K of end groups per unit area of membrane with configuration C_{III} which are bonded to a potassium ion is

(I.4.8)
$$n_K = (p_e[K]_e + p_i[K]_i)n'_{III}$$

where $[K]_e$ and $[K]_i$ are the concentrations of potassium in the extracellular medium and membrane interior, respectively, p_e and p_i denote the velocities of the ions in the respective media, and n'_{III} is the number of unbonded end groups with configuration C_{III} . Those end groups with configuration C_{II} were assumed to be weakly bonded to the sodium ions and therefore are not affected by the ionic environment present.

Having established a mathematical description for the configu-

rational changes and the effect of the ionic environment, the dynamic behavior of the ion exchange process occurring at the end groups is given by

$$(I.4.9) \quad \begin{cases} \dfrac{dn_I}{dt} = -(k_1 + k_6)n'_I + k_2 n_{II} + k_5 n'_{III} \\[2ex] \dfrac{dn_{III}}{dt} = k_6 n'_I + k_3 n_{II} - (k_4 + k_5)n'_{III} \\[2ex] n_{II} = n_{Na} = n_T - (n'_I + n_{Ca} + n'_{III} + n_K) \end{cases}$$

together with (I.4.6) - (I.4.8).

The ionic currents resulting from the transfer of ions at the end groups was determined in terms of the inward and outward ionic fluxes. In the case of potassium, the inward ionic flux is given by

$$(I.4.10) \qquad \overrightarrow{r}_K = \sigma_K n_K [K]_e \, e^{-\frac{W_{Ke}}{kT}}$$

and the outward flux is

$$(I.4.11) \qquad \overleftarrow{r}_K = \sigma_{Ki} n_K [K]_i \, e^{-\frac{W_{Ki}}{kT}}$$

where W_{Ke} and W_{Ki} represent the energies required to displace a bonded potassium ion, k is the Boltzmann's constant, T is the absolute temperature, and both σ_{Ke} and σ_{Ki} are constants which account for molecular velocity and membrane area factors. The resulting formulation for the potassium current I_K is

$$(I.4.12) \qquad I_K = qn_K\left[\sigma_{Ki}[K]_i\, e^{-\frac{W_{Ki}}{kT}} - \sigma_{Ke}[K]_e\, e^{-\frac{W_{Ke}}{kT}}\right]$$

where q is the electronic charge. Similarly the sodium current resulting from transfer of ions at the extracellular membrane surface is given by

$$(I.4.13) \qquad I_{Na} = qn_{Na}\left[\sigma_{Nai}[Na]_i\, e^{-\frac{W_{Nai}}{kT}} - \sigma_{Nae}[Na]_e\, e^{-\frac{W_{Nae}}{kT}}\right].$$

Since the membrane interior was assumed to be inert and continuous, upon reaching the interior the ion is only under the influence of electrical and concentration gradients. To this point only the permeability of cations has been considered. In the case of anions, permeability was assumed to be independent of the phosphate end groups and resulted entirely from diffusion. The permeable anion is therefore only affected by the electric and concentration gradients across the membrane. Thus the formulations for the ionic current of the anions, predominately chloride, and that for the cations in the membrane interior are analogous and given by the flow equations

$$(I.4.14) \qquad \begin{cases} I_K = q\alpha_K\left(\dfrac{\partial[K]}{\partial x} + [K]\dfrac{\partial\theta}{\partial x}\right) \\ I_{Na} = q\alpha_{Na}\left(\dfrac{\partial[Na]}{\partial x} + [Na]\dfrac{\partial\theta}{\partial x}\right) \\ I_{Cl} = q\alpha_{Cl}\left(\dfrac{\partial[Cl]}{\partial x} + [Cl]\dfrac{\partial\theta}{\partial x}\right) \end{cases}$$

where θ is the potential across the interior of the membrane, and α_K, α_{Na}, and α_{Cl} are the diffusion coefficients of the respective ions in the membrane. In addition, the continuity equation and Poisson's equation are also satisfied by the system. Hence

$$(I.4.15) \qquad \begin{cases} \dfrac{\partial I_K}{\partial x} = q \dfrac{\partial [K]}{\partial t} \\[2ex] \dfrac{\partial I_{Na}}{\partial x} = q \dfrac{\partial [Na]}{\partial t} \\[2ex] \dfrac{\partial I_{Cl}}{\partial x} = q \dfrac{\partial [Cl]}{\partial t} \end{cases}$$

and

$$(I.4.16) \qquad \frac{\partial^2 \theta}{\partial x^2} = - \frac{4\pi q^2}{DkT} ([K] + [Na] - [Cl])$$

where D is the dielectric constant for the membrane interior.

In order to examine the formulation presented by Goldman it is necessary to obtain approximations for the energy terms. Although the analysis is limited, approximate solutions show good agreement with experimental data for steady-state current-voltage relations and potassium tracer flux ratios.

The final model to be discussed in §I.4 was proposed by McIlroy (1970). In this theory the membrane permeability changes are determined by enzymatic activity. The model is of considerable interest since the formulation proposed for potassium conductance is formally

equivalent to that proposed by Hodgkin and Huxley (1952d), even though the mechanisms for membrane permeability changes in the two theories differ considerably.

McIlroy's model represents the extension of two previously obtained results. Bass and Moore (1968) observed that a critical depolarization of the squid axon membrane produces an increment in the membrane pH . Furthermore, an increment in membrane pH of such magnitude was found to be sufficient to initiate an action potential by nonelectrical means. In an attempt to associate changes in membrane pH with the changes in membrane permeability, Bass and McIlroy (1968) considered the effects of pH changes on enzymes. The model adopted for study was that of Michaelis-Davidsohn. For this model the enzyme possesses a neutral base and a singly charged base both of which can accept at most one proton in the formation of a cationic acid and neutral acid, respectively. The arrangements of the enzyme are denoted by $E_{p_c p_n}$ where p_c and p_n represent the number of protons on the neutral and singly charged bases, respectively. Of the four possible arrangements, E_{10} was assumed to be the only active form of the enzyme with respect to the enzymatic substrate. Bass and McIlroy succeeded in determining the fraction f of enzymes in active form as a function of the membrane pH . The formulation is given by

$$\text{(I.4.17)} \qquad f = \frac{[E_{10}]}{[E_{tot}]} = \left(1 + \frac{a^2}{4} + a \cosh y\right)^{-1}$$

where

(I.4.18) $$y = (pH - pH_{max})\ell n\ 10$$

and

(I.4.19) $$a = 2\left(\frac{K_c}{K_n}\right)^{\frac{1}{2}} .$$

The symbols $[E_{10}]$ and $[E_{tot}]$ denote the concentration of the active enzyme form and of all the enzyme forms, respectively, K_c and K_n are the dissociation constants of the cationic and neutral acid, respectively, and y is a measure of the ratio of proton concentration to that at which $f = f_{max}$. Using (I.4.17) - (I.4.19), Bass and McIlroy demonstrated that in the membrane medium the activity of suitably chosen enzymes undergo significant changes following the increment in membrane pH capable of producing an action potential. McIlroy extended these results by proposing a physical model in which enzymes under the influence of the membrane pH produce the membrane permeability changes.

The model for nerve excitation considered by McIlroy closely resembles that proposed by Nachmansohn (1959). For this theory, acetylcholine S, present in the membrane, acts as the substrate for an unidentified receptor enzyme R and the esterase enzyme H. At the resting membrane potential, acetylcholine is assumed to be stored in a lipid-bound form free from hydrolysis. Upon depolarization, the active form $^{R}E_{10}$ of the receptor enzyme combines with acetylcholine to form a receptor protein complex with the configurational form C_{open}. This configuration is reversibly converted to the configurational form

C_{closed} which produces the permeability changes responsible for the rising part of the action potential. Hydrolysis of the configurational form C_{open} of the receptor protein by the active form ${}^{H}E_{10}$ of the esterase results in the inactivation of the ionic currents. The dynamic behavior is determined by rate constants which govern each step of the procedure. The capture of acetylcholine by the receptor enzyme was assumed to proceed at a rate determined by the constant k_1 . Transformation of the configurational form C_{open} into C_{closed} is determined by the rate constant $\frac{1}{\tau_{conf}}$ while the reverse rate is given by $\frac{K_{conf}}{\tau_{conf}}$. The rate of hydrolysis is governed by the constant k_2 .

A quantitative description of potassium conductance was obtained by considering the membrane to contain specialized potassium specific permeability regions. In each region, potassium ions are permitted to pass through the membrane only if the region contains N receptor proteins of the configurational form C_{closed} . Hence potassium conductance g_K is given by

$$g_K = \overline{g_K}\,[C_{closed}]^N \tag{I.4.20}$$

where $[C_{closed}]$ is the concentration of the closed configuration of the receptor protein, and $\overline{g_K}$ is a constant. By considering the rate constants governing the process it is possible to determine the dynamic behavior of $[C_{closed}]$. The formulation for the dynamic behavior is

$$\tau_{conf}\frac{d}{dt}[C_{closed}] = -K_{conf}[C_{closed}] + [C_{open}] \tag{I.4.21}$$

and

$$\frac{d}{dt}\,[C_{tot}] = k_1[S]\left[{}^{R}E_{10}\right] - k_2\left[{}^{H}E_{10}\right][C_{open}] \tag{I.4.22}$$

where

$$[C_{tot}] = [C_{open}] + [C_{closed}] \tag{I.4.23}$$

$${}^{R}E_{10} = \frac{\left[{}^{R}E_{tot}\right] - [C_{tot}]}{1 + \frac{{}^{R}a}{4} + {}^{R}a\,\cosh\,({}^{R}y)} \tag{I.4.24}$$

$${}^{H}E_{10} = \frac{\left[{}^{H}E_{tot}\right]}{1 + \frac{{}^{H}a}{4} + {}^{H}a\,\cosh\,({}^{H}y)} \tag{I.4.25}$$

and

$$\left\{\begin{aligned} {}^{i}y &= (pH - {}^{i}pH_{max})\,\ell n\ 10 \\ {}^{i}a &= 2\left(\frac{{}^{i}K_c}{{}^{i}K_n}\right)^{\frac{1}{2}}, \qquad i = R,H\ . \end{aligned}\right. \tag{I.4.26}$$

The equation for $\left[{}^{R}E_{10}\right]$ given by (I.4.24) differs from that proposed by (I.4.17) since it is necessary to account for the effect of saturation of the receptor enzyme. This is accomplished by replacing $\left[{}^{R}E_{tot}\right]$ as proposed in (I.4.17) by $\left[{}^{R}E_{tot}\right] - [C_{tot}]$.

Certain physiological results permit the simplification of the formulation for potassium conductance. Examination of the time constants of voltage-clamp data associated with potassium conductance reveal it is

possible to consider $\tau_{conf} = 0$. Hence (I.4.21) is replaced by

(I.4.27) $$[C_{open}] = K_{conf}\,[C_{closed}] \ .$$

By letting

(I.4.28) $$n^{*} = \frac{[C_{open}]}{\left[{}^{R}E_{10}\right]}$$

equations (I.4.20) and (I.4.22) are respectively transformed to

(I.4.29) $$g_K = \overline{g_K}\left[{}^{R}E_{10}\right]^{N}\left(\frac{1}{K_{conf}}\right)^{N} n^{*N}$$

and

(I.4.30) $$\frac{dn^{*}}{dt} = \alpha^{*}\{1 - (1 + \frac{1}{K_{conf}})n^{*}\} - \beta^{*}n^{*}$$

where

(I.4.31) $$\alpha^{*} = \frac{k_1[S]}{\left(1 + \frac{{}^{R}a^{2}}{4} + {}^{R}a \cosh\left({}^{R}y\right)\right)\left(1 + \frac{1}{K_{conf}}\right)}$$

and

(I.4.23) $$\beta^{*} = \frac{k_2\left[{}^{H}E_{tot}\right]}{\left(1 + \frac{{}^{H}a^{2}}{e} + {}^{H}a \cosh\left({}^{H}y\right)\right)\left(1 + \frac{1}{K_{conf}}\right)}$$

McIlroy also determined that $K_{conf} >> 1$ in which case (I.4.30) is

further simplified to

$$\frac{dn^*}{dt} = \alpha^*(1 - n^*) - \beta^* n^* \; . \tag{I.4.33}$$

With $N = 4$, (I.4.29) and (I.4.33) are equivalent to (I.2.5), the equation proposed by Hodgkin and Huxley (1951d) for potassium conductance. This result is encouraging since no attempt was initially made to simulate the formulations obtained by Hodgkin and Huxley in the derivation of this enzyme model for nerve excitation.

The formulation for sodium conductance is identical to that for potassium conductance. Hence the same formulation (I.4.29), (I.4.31), (I.4.32), and (I.4.33) must be able to describe the different behaviors exhibited by the two conductances. The difficulty is resolved by assuming the enzymes associated with each conductance have different locations in the membrane. Those for potassium conductance are located at the interior of the membrane while those for sodium are located at the exterior of the membrane. By assuming that the values of the time constant for the return of the membrane pH to its resting level following a voltage-clamp depolarization differ significantly between the two regions, the differences between the behavior of potassium and sodium conductances are realized.

The models discussed in §I.2, §I.3 and §I.4 do not exhaust the possibilities which exist for mathematical models of nerve excitation. These models do, however, indicate the variety of approaches that are used in deriving the models. It has been suggested in §I.3 that certain

of the excitation models can be classified in terms of the structure of their mathematical formulation. Since it is possible to classify the models in terms of their mathematical formulations it may also be possible to determine a generalized mathematical formulation for nerve excitation. To obtain such a generalization it is necessary to examine the mathematical properties of the formulations for the different models. Much of the research on the mathematical structure of the formulations for nerve excitation models has been done by FitzHugh and will be reviewed in §I.5.

§I.5 Classification and Generalization of the Mathematical Models of Nerve Excitation

The fact the mathematical formulations provide a means to establish the validity of the proposed permeability mechanisms of each model demonstrates their usefulness in the study of the excitatory behavior of nerve. The importance of the mathematical formulations however is not restricted to this application alone. As pointed out in §I.3, by considering the structure of the equations it is possible to categorize the models on the basis of their formulation for certain of the basic qualitative features necessary for excitatory behavior. Employing the quantitative nature of the formulations in the investigation of these categories hopefully will provide a means to determine the exact nature of these basic features. In §I.4, this proposal was extended by suggesting that through the investigation of the structure and mathematical properties of the formulations it may be possible to derive a generalized formulation for the basic interactions required to describe the excitable behavior of the squid nerve axon. §I.5 is devoted to the classification, where it is possible, and generalization of the excitation models.

It is possible to classify certain of the models into two distinct categories on the basis of their formulation for sodium conductance. In the Hodgkin-Huxley theory, sodium conductance is a function of two independent variables which are each dependent on wholly

independent processes. For the theories proposed by Mullins (1959), Hoyt (1963), Goldman (1964) and McIlroy (1970) sodium conductance is a function of one variable which itself is dependent on two or more coupled processes. This qualitative mathematical distinction between the two categroies has been shown by Hoyt (1968) to lead to quantitative differences in their predictions of sodium conductance for different voltage-clamp potentials following a conditioning voltage-clamp. Conclusive experimental evidence, however, has not to this point been obtained which indicates which of the categories simulates the axon most accurately.

Certain of the models can also be categorized in terms of the interdependence, demonstrated in the formulation, between the sodium and potassium currents. The models proposed by Hodgkin and Huxley (1952d), Hoyt (1963) and McIlroy (1970) consider the sodium and potassium permeability changes to be independent of each other. The models of Mullins (1959) and Goldman (1964), however, consider the sodium and potassium permeability changes to be coupled. This coupling results from the assumption that both sodium and potassium ions share a common pathway through the membrane. Mullins (1968) conjectures that the hypothesis of a common pathway would be invalid if circumstances exist for which the sum of sodium and potassium conductance at a given time exceeds that of the maximum sodium conductance. Again, experimental evidences has not completely resolved which of the proposals is valid.

In order to obtain a generalized formulation for nerve

excitation, it was pointed out in §I.4 that the mathematical structure of the existing formulations must be investigated. FitzHugh, in a series of papers (FitzHugh, 1960 and 1961) analyzed the Hodgkin-Huxley equations in an attempt to determine the physiological importance of each of the dependent variables. The analysis was carried out using phase space methods.

To determine the significance of the dependent variables of the Hodgkin-Huxley equations and to reduce the four dimensional (V,m,h,n) phase space to one which can be graphically portrayed, FigzHugh (1960) reduced the system of equations by considering one or more of the dependent variables to be constant. It is possible to classify the variables V, m, h and n on the basis of the magnitude of their relaxation times which are given by

$$(\text{I.5.1}) \qquad \begin{cases} \tau = \dfrac{C_M}{g_K + g_{Na} + \overline{g_\ell}} \, , \\[2ex] \tau_m = \dfrac{1}{\alpha_m + \beta_m} \, , \\[2ex] \tau_h = \dfrac{1}{\alpha_h + \beta_h} \, , \\[2ex] \text{and} \quad \tau_n = \dfrac{1}{\alpha_n + \beta_n} \, , \end{cases}$$

respectively. Since the magnitude of τ_m and τ were determined to be approximately one-tenth the magnitude of τ_n and τ_h , FitzHugh

considered the Hodgkin-Huxley equations with n and h held constant at their resting state values. This reduced system of Hodgkin-Huxley equations is

$$
\text{(I.5.2)} \quad
\begin{cases}
I = C_M \frac{dV}{dt} + n_o^4(V - V_K) + m^3 h_o (V - V_{Na}) + \overline{g_\ell}(V - V_\ell) \\[2ex]
\frac{dm}{dt} = \alpha_m(1 - m) + \beta_m m \\[2ex]
\alpha_m(V) = \frac{0.1(V + 25)}{e^{\frac{V+25}{10}} - 1} \\[2ex]
\beta_m(V) = 4\, e^{-\frac{V}{18}}
\end{cases}
$$

where n_o and h_o denote the values of n and h at the resting membrane potential, $V = 0$.

The (V,m) phase plane of the reduced system (I.5.2) was determined by analogue computer. Trajectories in the plane represent the response to various magnitudes of instantaneous current impulse administered at $t = 0$. The reduced system admits only three singular points. Two of the singular points were determined to be stable. The third singular point, a saddle point, together with two stable separatrices form a boundary in the phase plane separating the two stable singular points. The strength of the initial current pulse determines on which side of these separatrices a trajectory lies and hence to which stable singular point it will approach. It is possible to correspond these

phase plane regions and points to physiological states of the squid nerve axon. The two stable separatrices together with the saddle point correspond to the threshold phenomena present in the squid axon, while the two stable singular points represent the physiological states of rest and excitation, respectively.

By removing the restrictions on n and h and considering the (V,m) phase plane for the complete Hodgkin-Huxley equations produces a number of changes. Only the stable singular point corresponding to the resting state remains. The threshold phenomena in this case is represented by a trajectory, for which only a portion of its length acts as a separatrix dividing the neighboring trajectories, which represent the responses to instantaneous current impulses, into subthreshold and full action potential responses. It was impossible, however, to find a unique separatrix which would distinguish between all the trajectories on the basis of this property. The (V,m) phase plane, therefore, demonstrates the inability of the Hodgkin-Huxley equations to satisfy the "all-or-none" law as demonstrated by the squid nerve axon. In contrast to the (V,m) phase plane with h and n constant, the (V,m) phase plane representing the complete Hodgkin-Huxley equations contains regions which correspond to the physiological states of recovery and refractoriness. Thus the pair of dependent variables V and m can be considered to represent the property of excitability of the axon while n and h represent the properties of recovery and refractoriness.

The Hodgkin-Huxley equations were considered by FitzHugh to

be a member of a class of non-linear systems which demonstrate excitable and oscillatory behavior. To further analyze the properties of the Hodgkin-Huxley equation, FitzHugh derived a mathematical model which would represent this class of non-linear systems and at the same time be more tractable than the Hodgkin-Huxley equations. The model was not designed to represent experimental data accurately but rather to represent the basic interactions required to produce the various physiological states of the squid axon.

The model proposed by FitzHugh is based on the van der Pol equation (van der Pol: 1926), for a relaxation oscillator given by

$$\frac{d^2x}{dt^2} + c(x^2 - 1)\frac{dx}{dt} + x = 0 \tag{I.5.2}$$

where c is a positive constant. Applying the Liénard transformation (Liénard; 1928)

$$y = \frac{1}{c}\frac{dx}{dt} + x - \frac{x^3}{3} \tag{I.5.4}$$

to (I.5.3) yields the set of differential equations

$$\left\{\begin{aligned} \frac{dx}{dt} &= c\left(y + x - \frac{x^3}{3}\right) \\ \frac{dy}{dt} &= -\frac{x}{c}\,. \end{aligned}\right. \tag{I.5.5}$$

The phase plane of (I.5.5) contains an unstable singular point at the origin. To remove this unstable singular point, FitzHugh considered the equations

$$(I.5.6)\qquad \begin{cases} \dfrac{dx}{dt} = c(y + x - \dfrac{x^3}{3} + z) \\[2ex] \dfrac{dy}{dt} = - (\dfrac{x - a + by}{c}) \end{cases}$$

with

$$(I.5.7)\qquad \begin{cases} 1 - \dfrac{2b}{3} < a < 1 , \\[2ex] 0 < b < 1 , \\[2ex] b < c^2 \end{cases}$$

and both a and b constant. In order to consider system (I.5.6) as a model for nerve excitation it was assumed that x denotes the displacement of the membrane potential from the resting potential and z denotes the membrane current density. System (I.5.6) is referred to in the literature as the Bonhoeffer-van der Pol equations.

FitzHugh analysized the Bonhoeffer-van der Pol equations by phase space methods using computer simulations. Conditions (I.5.7) had been chosen in order that for $z = 0$, the isoclines corresponding to $\frac{dx}{dt} = 0$ and $\frac{dy}{dt} = 0$ intersect at a unique point, which is stable. This singular point represents the resting state of the squid nerve axon. It was also possible to correspond other physiological states of the axon, such as the threshold phenomena and refractory period to specific regions of the phase plane. Furthermore, the electrical behavior of the axon under a variety of stimulus conditions could be adequately interpreted on the phase plane. However, for a step current of magnitude exceeding a critical value the trajectories in the phase plane approach a stable limit

cycle. Hence, the Bonhoeffer-van der Pol model produces an infinite train of impulses for constant current stimulation above a critical level, as did the Hodgkin-Huxley model. As pointed out in §I.2, this is contrary to the known behavior of the squid nerve axon.

The reduced system of (I.5.6) with y held constant was also considered by FitzHugh (1961). The x phase line of this reduced system contains three singular points. Two of the singular points are stable and represent respectively, the physiological states of rest and excitation. The third singular point, a saddle point situated between the two stable singular points, represents the threshold phenomena of the axon. There are, however, no regions in the x phase line which correspond to the recovery or the refractory period of the axon. The dependent variable x, therefore, represents nerve excitability and corresponds to the variables m and V of the Hodgkin-Huxley equations, while the variable y represents the states of recovery and refractoriness and corresponds to the variables n and h of the Hodgkin-Huxley equations. This final result provides a means for comparing the formulations proposed by Hodgkin and Huxley and by FitzHugh.

In order to compare the Hodgkin-Huxley equations and the Bonhoeffer-van der Pol equations it is necessary to obtain a phase plane of the Hodgkin-Huxley equations which can be compared to the (x,y) phase plane. To construct such a phase plane, FitzHugh utilized the previously obtained result which reveals the correspondence between the dependent variables of the two formulations. The resulting phase plane

is the (u,w) phase plane for which u is a function of m and V, and w is a function of n and h. The points (u,w) in the plane were determined in the following manner. Each value u corresponds to the points in the (m,V) plane for which $u = V - 36m$ while each value w corresponds to the points in the (n,h) plane for which $w = \frac{1}{2}(n - h)$. The projections in each case had been chosen in order to preserve the physiologically significant features represented on the respective planes.

The (u,w) phase plane of the reduced system of Hodgkin-Huxley equations, as with the (x,y) phase plane of the Bonhoeffer-van der Pol equations, contained regions and points which correspond to specific physiological states of the nerve. Furthermore, the (u,w) phase plane and the (x,y) phase plane were found to be qualitatively similar for a variety of stimulus current inputs. In particular, for both models the trajectories representing the response to stimulation by a step of sufficient magnitude, approach a stable limit cycle. These similarities suggest that the Hodgkin-Huxley and Bonhoeffer-van der Pol models can be considered as belonging to the same general class of excitable-oscillatory systems. FitzHugh (1961), however, expresses one reservation in making this correspondence between the two models. The objection is that the (u,w) plane is not a phase plane since in general there exist an infinite number of values of $\frac{du}{dt}$ and $\frac{dw}{dt}$ for each point (u,w). In spite of this reservation, the ability of the Bonhoeffer-van der Pol model to qualitatively describe the physiological states of the nerve and accurately predict certain excitable neural phenomena secures its relevance in neural modelling.

In 1969 FitzHugh attempted to derive a generalized mathematical model of squid nerve excitation. The basis of the mathematical formulation is the assumption that the squid axon membrane can be considered to consist of a capacitor in parallel with a conductor. Hence the basic equation is

$$\text{(I.5.8)} \qquad \frac{dV}{dt} = \frac{1}{C_M} [I - I_i]$$

where I, V, C_M, and t are as defined for the Hodgkin-Huxley equations and I_i is the current density per unit area of membrane through the conductor. Experimental evidence (Hodgkin and Huxley 1952) indicates the excitatory behavior of the axon can be attributed primarily to the behavior of the conductance current I_i. For the generalized formulation to exhibit the excitatory behavior of the nerve, FitzHugh proposed that I_i must be a function of variables which, as in the case of the dependent variables of the Hodgkin-Huxley and Bonhoeffer-van der Pol formulations, represent specific physiological states of the excitation process. The functional form of I_i was derived from the fact it is possible to classify the physiological states or events of excitation according to their duration time. The classifications considered by FitzHugh, listed in order of increasing time duration, are excitation events, recovery events and adaptation events. Excitation events include the threshold phenomena, and the rising phase of the action potential, while recovery events consist of the falling phase of the action potential and the refractory phase. Adaptation events, which develop the slowest, account for the reduction of the frequency and possible termination of a

train of impulses produced by a prolonged constant stimulation. The excitatory nerve behavior was, therefore, incorporated in the formulation by assuming I_i is a function of the membrane potential and one or more time dependent variables each of which can be classified according to the system devised for classifying physiological events of excitation. Thus the generalized mathematical formulation for nerve excitation is given by

$$\text{(I.5.9)} \quad \begin{cases} \dfrac{dV}{dt} = \dfrac{1}{C_M}[I - I_i(V,W_1,W_2,\ldots,W_\mu)] \\ \\ \dfrac{dW_j}{dt} = F_j(V,W_1,W_2,\ldots,W_\mu); \qquad j = 1,2,\ldots,\mu . \end{cases}$$

where each W_j for $j = 1,2,\ldots,\mu$ is either an excitation variable, recovery variable, or adaptation variable.

The mathematical models discussed in sections §I.1 through §I.5 with the exception of the model of Young (1937) for $b \neq 0$ can all be described by the system (I.5.9). It is of interest to classify, in accordance with FitzHugh's proposal, the variables of certain of these excitation models discussed. For the models of the two-factor theory of excitation, L is a recovery variable while K represents the membrane potential. For the model proposed by Hodgkin and Huxley (1952d) m is an excitation variable, and both n and h are recovery variables. In the case of the Bonhoeffer-van der Pol formulation (I.5.6) which can be transformed to the equivalent formulation

$$(I.5.10)\qquad \begin{cases} \dfrac{dV}{dt} = V - \dfrac{V^3}{3} - W + I \\ \\ \dfrac{dW}{dt} = \phi\ (V + a - bW) \end{cases}$$

with a, b, and ϕ constant and with the conventional notation for membrane potential and membrane current in excitation models, W is a recovery variable. Neither the Hodgkin-Huxley formulation nor the Bonhoeffer-van der Pol formulations contain adaptation variables. FitzHugh (1969) suggests that the absence of such variables is responsible for the formulation's production of an infinite train of impulses for step current stimulation of sufficient magnitude.

FitzHugh (1969) has attempted to extend the Hodgkin-Huxley and Bonhoeffer-van der Pol formulations to include adaptation variables. To obtain the required formulation it is necessary to reconsider the two-factor theory of excitation. As stated in §I.1, the two-factor theory with only one exception is unable to account for events following the initiation of an action potential. This exception, derived by Katz (1936), is the extension of Hill's model (Hill: 1936a) to enable the determination of the duration of a train of impulses. Katz proposed that if $k \ll \lambda$ in (I.1.5) and (I.1.7), then for stimulation by a step current of sufficient magnitude the local potential K would remain above the threshold L for a period of time during which repetitive impulses would occur. The effect of the assumption that $k \ll \lambda$ is to change variable L to an adaptation variable. This assumption also produces changes in the formulation proposed by Hill (1936a). For

$k << \lambda$ equation (I.1.5) is replaced by

$$K = K_o + cI \tag{I.5.11}$$

where $c = kb$, and by defining $Z = K - L$ Hill's formulation given by (I.1.5) and (I.1.7) reduces to

$$\frac{dZ}{dt} = c\,\frac{dI}{dt} + \frac{Z - Z_o}{\lambda} \tag{I.5.12}$$

where $Z_o = K_o - L_o$. In the case of stimulation by a step current of magnitude I_1 administered at $t = 0$, (I.5.12) is given by

$$\frac{dZ}{dt} = cI_1\delta(t) - \frac{Z - Z_o}{\lambda} , \tag{I.5.13}$$

where $\delta(t)$ is the Dirac delta function, and has solution

$$\begin{cases} Z_o & ; \quad t \leq 0 \\ Z_o + cI_1 e^{-\frac{t}{\lambda}} & ; \quad t > 0 \end{cases} \tag{I.5.14}$$

According to Katz' assumption, repetitive impulses occur when $K = K - L > 0$. By (I.5.14), repetitive impulses occur only if $cI_1 > -Z_o$ and only during the time interval $0 < t < t_1$ where

$$t_1 = \lambda\, \ell n \frac{-cI_1}{Z_o} \tag{I.5.14}$$

is the duration of the train of impulses. This Hill-Katz model can be used to introduce adaptation variables into an excitation model by assuming that $Z - Z_o$ is the effective stimulating current instead of I and that $- Z_o$ is the threshold for repetitive behavior. In applying

this procedure to the Hodgkin-Huxley formulation, FitzHugh (unpublished) succeeded in producing only a finite train of impulses to stimulation by step current irrespective of its magnitude. This procedure does not, however, resolvee the problem completely since it is impossible to stimulate all experimentally observed features of a finite train of impulses (FitzHugh: 1969).

In §I.2 it was pointed out that the Hodgkin-Huxley equations are a model for the squid nerve axon with the experimentally induced condition of a uniform membrane potential over the entire axon membrane. This interpretation also applies to the models of excitation considered in §I.3, §I.4 and §I.5 including the generalized model. The models of excitation are therefore restricted in three major ways. First, the formulations do not take into account the passive electrical behavior of the membrane to electrical stimulus. Secondly, since the squid nerve axon is a representative of only one class of excitable tissue, the models do not necessarily apply to other excitable tissue which is structurally different from that of the squid nerve. Finally all the models account for nervous stimulation in terms of an electrical stimulation administered to the axon. Thus the models neglect to account for the effect of the soma-dendritic, through which the nerve normal receives stimulation, on the excitable behavior of the nerve. The three remaining sections of Chapter I describe the attempts which have been made to overcome these three restrictions of the excitation model.

§I.6 Mathematical Models of Action Potential Propagation

To this point the models of nerve excitation have been restricted to the special case for which the membrane potential is assumed to be uniform over the entire axon. The models have not included the passive electrical properties of the nerve resulting from the administration of a stimulating current. Normally during the application of an external current at a point on the squid nerve, there are circulating currents which flow along and through the membrane. It is these circulating currents which account for the propagation over the entire nerve of an action potential initiated at a point on the axon.

The distribution of the membrane potential over the membrane of the squid nerve axon has been modelled by assuming the axon possesses the properties of a core conductor. To obtain the mathematical description, the axon is considered to be a cyclindrical cable-like structure of infinite length consisting of a conducting core, the axoplasm, which is separated from the extracellular conducting medium by a resistive and capacitative sheath, the nerve membrane.

A number of assumptions have been placed on this basic model in order to simplify the mathematical formulation. First, the axoplasm and extracellular fluid are considered to be ohmic conductors. Secondly, by assuming the axon to be sufficiently thin and the axoplasmic and extracellular fluid resistances to be low compared with the membrane

resistance it is possible to ignore the radial currents in both media. This restriction permits the three dimensional problem to be considered in one dimension. Both assumptions have been shown not to introduce serious errors in the calculations (Hodgkin and Rushton: 1946). A further simplification results by considering the extracellular medium to be of sufficient volume in order that the extracellular fluid is essentially isopotential. This final assumption makes it possible to neglect the extracellular fluid resistance which will be negligible under the circumstances (Noble: 1966).

With these assumptions, the current i_a flowing through the axoplasm is parallel to the axon and is related to V, the displacement of the membrane potential from the resting potential, by Ohm's law. Hence

$$\frac{\partial V}{\partial x} = - i_a r_a \tag{I.6.1}$$

where x is the distance along the axon, and r_a is the resistance of the axoplasm per unit length of axon. Kirchhoff's law

$$\frac{\partial i_a}{\partial x} = j_M , \tag{I.6.2}$$

where j_M is the membrane current density per unit length of axon, is satisfied at all points on the axon except where the external stimulus is applied. Equations (I.6.1) and (I.6.2) can be combined to yield

$$j_M = \frac{1}{r_a} \frac{\partial^2 V}{\partial x^2} \tag{I.6.3}$$

for which the boundary conditions are given by

(I.6.4)
$$\left\{\begin{array}{l} V = 0 \quad \text{at} \quad t = 0 \quad \text{for} \quad -\infty < x < \infty \\ \text{and} \\ \lim\limits_{x\to\pm\infty} V(x,t) = 0 \quad \text{for} \quad 0 \leq t < \infty \;. \end{array}\right.$$

For practical application it is convenient to reformulate (I.6.3) in terms of more basic quantities. This is accomplished by defining

(I.6.5)
$$\left\{\begin{array}{l} j_M = \pi d I \\ \text{and} \\ r_a = \dfrac{4\rho}{\pi d^2} \end{array}\right.$$

where d is the diameter of the axon, ρ is the specific resistivity of the axoplasm, and I is the membrane current density per unit area of membrane. The formulation for the distribution of the membrane potential over the axon is therefore given by

(I.6.6)
$$I = \frac{d}{4\rho} \frac{\partial^2 V}{\partial x^2} \;.$$

It is possible to make (I.6.6), the cable equation, more explicit by expressing the membrane current I in terms of its constituent parts. Since the membrane can be considered to consist of a capacitor and conductor in parallel, then (I.6.6) can be expanded to

(I.6.7)
$$\frac{d}{4\rho} \frac{\partial^2 V}{\partial x^2} + C_M \frac{\partial V}{\partial t} + I_i + I_s$$

where C_M is the capacity of the membrane per unit area, I_i is the ionic current density and I_s is the current density of the applied external current. A special case of (I.6.7) is that of a linear cable, for which I_i is a linear function of V. In this case if it is assumed that the external current is applied at $x = 0$, then at each point $x \neq 0$ the membrane potential is determined by

$$\frac{d}{4\rho}\frac{\partial^2 V}{\partial x^2} = C_M \frac{\partial V}{\partial t} + \frac{V}{R_M} \tag{I.6.8}$$

Where R_M is the membrane resistance per unit area of membrane. To solve (I.6.8) it is convenient to consider the transformation determined by defining

$$\left\{ \begin{array}{l} X = \dfrac{x}{\lambda} \\ \text{and} \\ T = \dfrac{t}{\tau} \end{array} \right. \tag{I.6.9}$$

where $\tau = R_M C_M$ is the membrane time constant and $\lambda = \sqrt{\frac{R_M d}{4\rho}}$ is the membrane space constant. The resulting transformation of (I.6.8), given by

$$\frac{\partial^2 V}{\partial X^2} - \frac{\partial V}{\partial T} - V = 0 , \tag{I.6.10}$$

is amenable to solution by Fourier transform methods. An important application of cable equation (I.6.10) will be considered in §I.8.

To model the behavior under electrical stimulation of a squid nerve axon, for which the membrane potential is not uniformly maintained

over the entire axon, it is necessary to consider not only the excitable properties of the nerve but also the passive electrical properties. Under these circumstances the mathematical formulation describing the axon results by combining the cable equation which determines the passive behavior of the nerve to electrical stimulation with a formulation describing the excitatory behavior.

By combining cable equation (I.6.6) with the Hodgkin-Huxley equations, Hodgkin and Huxley (1952d) attempted to calculate the form of an action potential which is propagated along the axon. This system of equations is equivalent to considering the Hodgkin-Huxley equations with (I.1.4) replaced by the partial differential equation

$$\text{(I.6.11)} \qquad \frac{d}{4\rho}\frac{\partial^2 V}{\partial x^2} = C_M \frac{\partial V}{\partial t} + I_K + I_{Na} + I_\ell \quad .$$

The set of equations consisting of (I.6.11) and (I.1.5) - (I.1.12) is referred to as the Hodgkin-Huxley partial differential equations. To reduce the difficulties of solving the partial differential equation (I.6.11), Hodgkin and Huxley considered only the steady state propagation of the action potential for which the wave form and velocity are constant. For steady-state propagation, (I.6.6) is replaced by

$$\text{(I.6.12)} \qquad I = \frac{d}{4\rho\theta^2}\frac{\partial^2 V}{\partial t^2}$$

where θ is the constant velocity of the propagated action potential and (I.6.11) of the Hodgkin-Huxley partial differential equations is replaced by the ordinary differential equation

(I.6.13)
$$\frac{d}{4\rho\theta^2}\frac{\partial^2 V}{\partial t^2} = C_M \frac{\partial V}{\partial t} + I_{Na} + I_K + I_\ell \ .$$

Using the numerical methods of Hartree (1932-33) to solve the system of equations (I.6.13) and (I.1.5) - (I.1.12), Hodgkin and Huxley (1952d) determined that the form, amplitude and velocity of the calculated propagating action potential are in close agreement with experimentally recorded propagating action potentials.

Further analysis of the Hodgkin-Huxley partial differential equation with (I.6.13) substituted for (I.6.11) has been carried out by Huxley (1959a,b) using a digital computer. In particular, the effect of temperature on the conduction velocity was calculated. Hodgkin and Huxley (1952d) had determined that in order for the Hodgkin-Huxley equations to include the effect of temperature variation on the nerve, each of the rate constants α_n, β_n, α_m, β_m, α_h and β_h must be multiplied by the factor

(I.6.14)
$$\psi = 3^{\frac{T-6.3}{10}}$$

where T denotes the temperature. The numerical solution of the system of equations (I.6.12) and (I.1.5) - (I.1.12) with the modification required to incorporate the effect of temperature, indicates there exists a critical value ψ_c of ψ such that for $\psi > \psi_c$ the propagation of an action potential can not occur (HUxley: 1959a). Furthermore, for $\psi < \psi_c$ two solutions in addition to that corresponding to the normal propagated action potential were obtained (Huxley: 1959b). One of these solutions

represents a low amplitude propagated action potential, while the other represents an infinite train of oscillations which are propagated along the axon. Both responses are conducted at a velocity lower than that for the normal propagated action potential. Neither response has been observed experimentally.

FitzHugh (1969) examined the propagation of an action potential using the Bonhoeffer-van der Pol equation (I.5.10) as the formulation describing nerve excitation. The model was restricted to the case of the steady state propagation. Thus the required formulation is

$$\text{(I.6.15)} \qquad \begin{cases} \dfrac{d}{4\rho\theta}\dfrac{\partial^2 V}{\partial t^2} = \dfrac{\partial V}{\partial t} - V + \dfrac{V^3}{3} + W \\[2ex] \dfrac{\partial W}{\partial t} = \phi(V + a - bW) \end{cases}$$

The numerical solution of (I.6.15) determined by digital computer simulations demonstrates there exists a critical value ϕ_c of ϕ such that for $\phi > \phi_c$ it is impossible for an action potential to propagate. For each $\phi < \phi_c$ there are two distinct solutions of (I.6.15). One solution corresponds to a normal propagated action potential. The second solution, a low amplitude action potential propagated at a velocity lower than that of the normal action potential, is similar to the solution determined by Huxley (1959b) for the system of equations (I.6.13) and (I.1.5) - (I.1.12). Hence ϕ appears to play the same role in the Bonhoeffer-van der Pol equations as the factor ψ, given by (I.6.14) does in the Hodgkin-Huxley equations.

In order to be able to quantitatively describe the initiation of an action potential at the point of stimulation and its subsequent propagation along the axon, the restriction that the action potential is propagated at a constant velocity and waveform must be removed. Therefore it is necessary to obtain the solution to a formulation consisting of an excitation equation together with cable equation (I.6.6) or one of its equivalent forms. A digital computer solution to such a formulation, the Hodgkin-Huxley partial differential equations, has been obtained by Cooley and Dodge (1966). The solution was determined by approximating (I.6.12) with a finite difference equation.

To obtain this approximation, a squid nerve axon of finite length was assumed to be represented on the one-dimensional x-axis by the interval $[0,x_{K+1}]$. This interval was then partitioned into $K+1$ subintervals each of length δx. It was supposed that over each subinterval k $(k = 0,1,2,3,\ldots,K)$ the membrane potential is uniform and is determined by the Hodgkin-Huxley equations appropriately subscribed to distinguish individual subintervals. If the external stimulus is administered at the point $x = 0$, then the boundary condition for each subinterval k $(k = 1,2,3,\ldots,K)$ is

$$I_k = \frac{d}{4\rho}\,\frac{V_{k-1} - 2V_k + V_{k+1}}{\delta x}$$

(I.6.16) where

$$V_{K+1} = 1$$

d is the axon diameter, ρ is the specific resistivity of the axoplasm,

I_k is the membrane current density for the k^{th} subinterval, and V_{k-1}, V_k and V_{k+1} are the membrane potentials for the $k-1$, k^{th}, and $k+1$ subintervals, respectively. To account for the external stimulus applied at $x = 0$, the boundary condition for the subinterval $k = 0$ is

$$I_o = \frac{1}{\delta x}\left[\frac{j_s}{d} - \frac{d}{2\rho}\frac{(V_o - V_1)}{\delta x}\right] \qquad \text{(I.6.17)}$$

where j_s is the stimulus current density per unit area of membrane and I_o, V_o, V_1, d and ρ are as defined in (I.6.16).

The solution to this finite difference approximation of the Hodgkin-Huxley partially differential equation with boundary conditions (II.6.16) and (II.6.17) is obtained by numerical integration with respect to t. The computed results for a propagating action potential have been compared with those obtained by Hodgkin and Huxley for a prapagating action potential with constant wave form and velocity. The two calculations agreed in regard to the peak amplitude and duration of the axon potential. Differences were however noted in the exponentiation rate in the foot of the rising phase.

Before attempting to derive excitation and propagation models for excitable tissue other than the squid nerve axon, in §I.7, it is of mathematical interest to consider the formulation for a generalized propagation equation. This generalization follows from combining the generalized excitation formulation (I.5.9) and cable equation (I.6.6). The resulting formulation is

$$\text{(I.6.18)}\quad \begin{cases} \dfrac{\partial V}{\partial t} - \dfrac{d}{4C_{M\rho}}\dfrac{{}^{2}V}{\partial x^{2}} = \dfrac{1}{C_M}\,[I_i(V,W_1,W_2,\ldots,W\ )] \\[2ex] \dfrac{\partial W_j}{\partial t} = F_j(V,W_1,W_2,\ldots,W\ );\quad j = 1,2,\ldots,\ \ . \end{cases}$$

In order to analyze this system, Evans and Shenk (1970) have considered the simplified system

$$\text{(I.6.19)}\quad \begin{cases} \left(\dfrac{\partial}{\partial t} - \dfrac{\partial^{2}}{\partial x^{2}}\right)V = I_i(V,W) \\[2ex] \dfrac{\partial W}{\partial t} = F(V,W)\quad . \end{cases}$$

Evans and Shenk have shown that with initial conditions

$$\text{(I.6.20)}\quad \begin{cases} V(x,0) = \phi(x) \\ \text{and} \\ W(x,0) = \psi(x) \end{cases}$$

the solution of (I.6.19) is exactly the solution of the system of integral equation

$$\text{(I.6.21)}\quad \begin{cases} V(x,t) = \displaystyle\int_{-\infty}^{\infty} G(x,y,t)\phi(y)dy \\[2ex] \qquad + \displaystyle\int_{0}^{t}\int_{-\infty}^{+\infty} G(x,y,t-s)I_i(V(y,s),W(y,s))dyds \\[2ex] W(x,t) = \ (x) + \displaystyle\int_{0}^{t} F(V(x,s),W(x,s))ds \end{cases}$$

where

(I.6.22) $$G(x,y,t) = \frac{1}{2\sqrt{\pi t}} e^{-\frac{(x-y)^2}{4t}}$$

Furthermore, the continuous dependence of the solutions on the initial values was established and solutions with initial values in a restricted range were shown to remain in the range for all time (Evans and Shenk: 1970).

§I.7 Mathematical Models of Excitation and Propagation in Myelinated Nerve

The squid nerve axon is a representative of only one type of excitable tissue. For other excitable tissue, which differ structurally from that of the squid nerve axon, the Hodgkin-Huxley equation have been successfully modified to describe the excitable behavior.

In vertebrates, the axons of certain nerves are covered except for small regions, called nodes of Ranvier, by a insulating myelin sheath. This insulating sheath restricts the excitable membrane of the axon to the nodes of Ranvier. Voltage-clamp analysis for a node of Ranvier of a myelinated Xenopus laevis nerve reveals certain similarities between this myelinated axon and the squid nerve axon (Frankenhaeuser: 1959, 1960, and 1962). In both nerves the membrane current consists of a capacitance current and an ionic current. Furthermore, the components of the ionic current found in the squid nerve axon are also present in the myelinated toad nerve axon.

Frankenhaeuser did however find important differences between the voltage-clamp data for the myelinated nerve and that for the unmyelinated nerve. It is these differences which account for the modification of the Hodgkin-Huxley equations required to make the formulation applicable to the myelinated nerve. In addition to the three components of the ionic current which are common to both nerves, a fourth component, a nonspecific ionic current I_p carried predominantly

by sodium ions, was found to be present at the node of Ranvier. Hence for the myelinated axon the membrane current density I per unit area of membrane is defined by

$$(I.7.1) \qquad I = C_M \frac{dV}{dt} + I_K + I_{Na} + I_\ell + I_P$$

for which the notation is defined in the Hodgkin-Huxley equations. The most significant difference between the two nerve types is that the instantaneous current-voltage relationship for the myelinated nerve is linear only in the case of the leakage current. For the sodium, potassium, and nonspecific currents, this relationship is most accurately described by the constant field equations of Goldman (1943) which in the case of the sodium current is

$$(I.7.2) \qquad I_{Na} = P_{Na} \frac{E_M F^2}{RT} \frac{[Na]_o - [Na]_i \, e^{\frac{E_M F}{RT}}}{1 - e^{\frac{E_M F}{RT}}}$$

where $[Na]_o$ and $[Na]_i$ are the concentrations of sodium in the extracellular medium and axoplasm, respectively, P_{Na} is the sodium permeability, F is Faraday's constant, R is the gas constant and T is the absolue temperature. I_K and I_P are given by expressions similar to (I.7.2) which contain the appropriate concentrations and permeabilities.

By (I.7.2), the permeabilities P_{Na}, P_K, and P_p at a given time are independent of the membrane potential. Therefore in considering the sodium, potassium and nonspecific ionic currents, it is more

appropriate to use the permeability rather than the conductance to describe the state of the respective ionic currents. As in the case of the conductances, the permeabilities P_K, P_{Na} and P_p are functions of both time and the membrane potential. To determine the functions $P_K = P_K(t)$ and $P_{Na} = P_{Na}(t)$ at a given membrane potential Frankenhaeuser used the formulations for $g_K = g_K(t)$ and $g_{Na} = g_{Na}(t)$ of the Hodgkin-Huxley equations as a guide line. The resulting equations are

(I.7.3)
$$\left\{\begin{aligned} P_K &= \overline{P_K}\, n^2 \\ \frac{dn}{dt} &= \alpha_n(1 - n) - \beta_n n \end{aligned}\right.$$

and

(I.7.4)
$$\begin{aligned} P_{Na} &= \overline{P_{Na}}\, hm^3 \\ \frac{dm}{dt} &= \alpha_m(1 - m) + \beta_m m \\ \frac{dh}{dt} &= \alpha_h(1 - h) + \beta_h h \end{aligned}$$

respectively, where $\overline{P_K}$ and $\overline{P_{Na}}$ are constants, and $0 \leq n,m,h \leq 1$. The formulation for $P_p = P_p(t)$ at a given membrane potential, which both satisfies the experimental data and is of the form of a Hodgkin-Huxley conductance equation, is

(I.7.5)
$$\left\{\begin{aligned} P_p &= \overline{P_p}\, p \\ \frac{dp}{dt} &= \alpha_p(1 - p) + \beta_p(p) \end{aligned}\right.$$

where $\overline{P_p}$ is a constant and $0 \leq p \leq 1$. As is the case for the conductances of the Hodgkin-Huxley formulation, the dependence of the permeabilities on the membrane potential is determined by the rate coefficients α_i and β_i for $i = n,m,h,p$. The formulations for the rate coefficients, as functions of the membrane potential, were empirically determined and are given by

$$(I.7.6)\quad \begin{cases} \alpha_i = \dfrac{A(V - B)}{1 - e^{\frac{B-V}{C}}} & \text{for} \quad i = m,n,p \\[2ex] \beta_i = \dfrac{A(B - V)}{1 - e^{\frac{V-B}{C}}} & \text{for} \quad i = m,n,p \\[2ex] \alpha_h = \dfrac{A(B - V)}{1 - e^{\frac{V-B}{C}}} & \\[2ex] \text{and} & \\ \beta_h = \dfrac{A}{1 + e^{\frac{B-V}{C}}} & \end{cases}$$

where A, B and C are constants and V is the displacement of the membrane potential from the resting potential.

Using this formulation (I.7.1) - (I.7.6), Frankenhaeuser and Huxley (1964) computed the membrane currents and potential changes occurring during a membrane action potential. The resulting computer simulations were in close agreement with the experimentally recorded results.

The method of propagation of a nerve action potential in a myelineated nerve differs significantly from that for an unmyelinated nerve. For the myelinated nerve the insulating qualities of the myelin sheath restricts the generation of membrane current to the region of the nodes of Ranvier. Hence during the propagation of an action potential the excitation jumps from node to node.

For the purposes of theoretical treatment, the myelinated axon is considered to consist of passive electrical segments, representing the internode lengths of myelin, separated from each other by short isopotential areas of excitable membrane, representing the nodes. To obtain the mathematical description of the propagation of an action potential in the myelinated nerve, Goldman and Albus (1968) represented a Xenopus laevis nerve by the one dimensional x-axis such that there is a node at $x = 0$ and the rest are evenly spaced with internodal distance L. By assuming the axon is symmetric with respect to the origin where the external stimulus current is applied, only non-negative values of x need to be considered.

At each node k $(k = 0,1,2,3,...)$ the membrane potential is determined by equations (I.7.1) - (I.7.6) with appropriate notation to distinguish the individual nodes. The passive electrical segments were assumed to be a linear core conducting cable. In order to apply cable equation (I.6.11) to describe the distribution of the membrane potential over the internodal segments, modifications are required to account for the resistance and capacitance of the myelin sheath. The internodal

myelin sheath consists of a Schwann cell which has been repeatedly wrapped around the nerve axon. The radial resistance and capacitance per unit length of axon resulting from such a structure are given by

(I.7.7)
$$r = k_1 \ \ln \frac{D}{d} \quad \text{and} \quad c = k_2 \ \ln \frac{D}{d}$$

respectively, where k_1 and k_2 are constants which account for resistance and capacitance of each layer as well as the number of layers. In (I.7.7), D denotes the diameter of the axon including the myelin while d is the diameter of the axon excluding the myelin. Hence the cable equation for the internode segment is

(I.7.8)
$$\frac{\pi d^2}{4\rho} \frac{{}^2 V}{x^2} = c \frac{V}{t} + \frac{V}{r}$$

for which the definition of V, ρ , and x are given in (I.6.11). To complete the mathematical description of the myelinated nerve it is necessary to consider the boundary and continuity conditions at each node. For $k \neq 0$, the boundary condition for (I.7.8) at the k^{th} node is

(I.7.9)
$$i_k = \left(\frac{\pi d^2}{4\rho} \lim_{x \to kL_+} \frac{\partial V}{\partial x} - \lim_{x \to kL_-} \frac{\partial V}{\partial x} \right) ; \qquad k = 1,2,3,\ldots$$

where i_k is the membrane current. At the origin $x = 0$, the node corresponding to $k = 0$, the boundary condition for (I.7.8) is

(I.7.10) $$i_o = \frac{\pi d^2}{4\rho}\left(r_e i_s + 2 \lim_{x\to 0} \frac{\partial V}{\partial x}\right)$$

where i_s is the externally applied stimulus current at $x = 0$ and r_e is the resistance per unit length of axon of the extracellular medium. To ensure the continuity of the potential over the entire axon it was assumed that

(I.7.11) $$\lim_{x\to kL} V(x,t) = V_k(t) \quad \text{for} \quad k = 0,1,2,3,\ldots$$

where $V_k(t)$ is the membrane potential at the k^{th} node.

By assuming the ratio of the axon diameter d to myelinated axon diameter D to be constant, and the internode length L to be proportional to the myelinated axon diameter D, as is the case for the myelinate nerve, Goldman and Albus carried out a dimensional analysis of the theoretical nerve. The computed results demonstrated that the propagation velocity of an action potential is porportional to the myelinated axon diameter D, in agreement with the experimental results for the myelinated nerve.

The myelinated nerve axon is not the only type of excitable tissue for which a modified form of Hodgkin-Huxley has been successfully applied. Brady and Woodbury (1957) have succeeded in modifying the equations to describe the excitable behavior of the ventricular fibers of cardiac muscle of frog. Using an entirely different formulation from that of Brady and Woodbury, Noble (1960 and 1962) was able

to describe the behavior of the mammalian Purkinje fibers for cardiac muscle.

§I.8 Mathematical Models of the Significance of the Soma-Dendritic Region on the Nerves Excitability

For the models considered in §I.1 - §I.7 nervous stimulation has been assumed to be an electrical stimulus administered to the axon of the nerve. In vivo, however, a nerve receives stimulation through its dendritic and soma region, from other nerves. On this basis the nerve can be functionally divided into the axon portion and the soma-dendritic portion. The models of excitation and propagation presented in the preceding sections are models related exclusively with the function associated with the axon protion of the nerve. In §I.8 two mathematical theories are presented which model the structural and functional relationship of the soma-dendritic portion of the nerve to the excitability of the nerve.

In a neural system consisting of many nerves, the axon of one nerve will terminate on the dendritic and somatic regions of other nerves. The region of close contact between the axon of one nerve and the soma and dendrites of another is known as the synapse. The influence of the presynaptic nerve on the dendrites and soma of the postsynaptic nerve can be transmitted by either electrical or chemical means. In the case of a "chemical synapse", the propagation of an action potential along the presynaptic axon results in the release of a specific chemical from the presynatic membrane which produces permeability changes in the postsynaptic membrane at the synapse. These permeability changes

result in ionic currents which may alter the membrane potential in the neighborhood of the synapse. If the membrane potential is changed then this increment in potential, called the postsynaptic potential, will passively spread over the rest of the nerve membrane. Its distribution in terms of time and distance will be determined by the membrane resistance and capacity. (Mountcastle: 1968).

There are two types of postsynaptic potentials each of which is determined by the character of the presynaptic nerve. The excitatory postsynaptic potential (EPSP), which is generated by an excitatory presynaptic nerve, is a depolarizing potential. The effect of EPSP's are summed both spatially and temporally. If an EPSP or the sum of a number of EPSP's attain an amplitude such that a critical level of depolarization is reached at the trigger zone of the nerve associated with the soma or axon, then a propagating action potential is generated. The other type of postsynaptic potential is an inhibitory postsynaptic potential (IPSP), which is produced at a synapse by an inhibitory presynaptic nerve. The IPSP can be either a depolarizing or hyperpolarizing potential depending on the value of the membrane potential. The effect of an IPSP is to reduce the excitability of the nerve. As in the case of EPSP's, the effect of IPSP's can be summed spatially and temporally.

In many nerves the dendrites are branched in complex geometrical structures. Since the effect of the postsynaptic potentials decays with both time and distance then different spatio-temporal patterns of

synaptic activity on such dendrites and the associated soma would seem to have different effects at the trigger zone and hence on nerve excitation (Rall: 1962). Two mathematical models which permit the prediction of the effect of various spatio-temporal patterns of synaptic activity have been proposed by Rall (1962, 1964).

The experimental evidence of ionic permeability changes and currents at the synapse suggest that a uniform patch of dendritic membrane can be described by an equivalent electrical circuit. (Coombs, Eccles and Fatt: 1955). The model for the dendritic membrane proposed by Rall (1962) consists of a capacitor in parallel with three separate parallel conductors. The three conductors represented three separate ionic pathways associated with the resting membrane potential, the EPSP, and the IPSP, respectively. For this circuit the mathematical formulation relating the membrane potential and membrane current of a unit patch of dendritic membrane was proposed by Rall (1962) to be

$$\text{(I.8.1)} \qquad I = C_M \frac{DE_M}{dt} + G_r(E_M - E_r) + G_\epsilon(E_M - E_\epsilon) + G_j(E_M - E_j)$$

where r, ϵ and j represent the ionic pathway associated with the resting membrane, the EPSP, and the IPSP, respectively. G_r, G_ϵ and G_j denote the respective separate conductances per unit area of membrane, and E_r, E_ϵ and E_j denote the equilibrium potentials of the respective pathways. E_M is the membrane potential, C_M is the membrane capacitance per unit area of membrane and I is the membrane current density per unit area of membrane. For the model C_M, G_r, G_ϵ, G_j, G_r, E_ϵ and E_j

were assumed to be constant with respect to time and membrane potential. To apply (I.8.1) it was reformulated into the equivalent form given by

$$IR_M = \tau \frac{dV}{dt} + k^2(V - V^*) \tag{I.8.2}$$

where

$$\left\{ \begin{aligned} &\tau = R_M C_M \quad \text{and} \quad R_M = \frac{1}{G_r} \\ &V = E_M - E_r \\ &k^2 = \frac{G_r + G_\epsilon + G_j}{G_r} \\ &\text{and} \\ &V^* = \frac{G_\epsilon(E_\epsilon - E_r) + G_j(E_j - E_r)}{k^2 G_r} \end{aligned} \right. \tag{I.8.3}$$

In order to reduce the difficulty of determining the distribution of the membrane potential over a branched dendritic tree, Rall (1962) considered a special class of dendritic trees which are mathematically equivalent to a cylindrical conducting core. To obtain this particular class, each dendritic tree is categorized in terms of the number n of equal branches of common radius r which are at a distance x from the soma. It had been assumed the cross section of the branches are circles, but the branches are not necessarily considered to be cylinders.

To derive this classification, it is necessary to determine

the distribution of the membrane potential over a theoretical dendritic tree. The mathematics are simplified by assuming that the extracellular medium is isopotential and that in the intracellular medium of the branches, the radial current flow is sufficiently small to be neglected. In this case, the combined longitudinal intracellular current i_d for n dendritic branches with common radius r at a distance x from the soma is

$$i_d = \frac{n\pi r^2}{\rho_d}\left[-\frac{\partial V}{\partial x}\right] \tag{I.8.4}$$

where ρ_d is the specific resistivity of the intracellular fluid of the dendrites. Furthermore, for these n branches the combined membrane current density I per unit area of membrane is given by

$$I = \left[-\frac{\partial i_d}{\partial x}\right]\left[\frac{dA}{dx}\right]^{-1} \tag{I.8.5}$$

where

$$\frac{dA}{dx} = 2\pi rn\frac{ds}{dx}\ , \tag{I.8.6}$$

$$\frac{ds}{dx} = \left[1 + \left(\frac{dr}{dx}\right)^2\right]^{\frac{1}{2}} \tag{I.8.7}$$

and A is the membrane surface area of each of the branches. By differentiating (I.8.4) with respect to x and making the appropriate substitutions given by (I.8.5) and (I.8.6), transforms (I.8.4) to

$$IR_M = \left[\frac{rR_M}{2\rho_d}\right]\left[\frac{ds}{dx}\right]^{-1}\left[\frac{\partial^2 V}{\partial x^2} + \frac{\partial V}{\partial x}\frac{d}{dx}\ell n\ (r^2 n)\right]\ . \tag{I.8.8}$$

The change of variable given by

$$\frac{dZ}{dx} = \left[\frac{rR_M}{2\rho_d}\right]^{-\frac{1}{2}} \left[\frac{ds}{dx}\right]^{\frac{1}{2}} \tag{I.8.9}$$

transforms (I.8.8) to

$$IR_M = \frac{\partial^2 V}{\partial Z^2} + \left(\frac{dZ}{dx}\right)^{-1} \frac{d}{dx} \ln\left[r^{\frac{1}{2}} n \left(\frac{ds}{dx}\right)^{\frac{1}{2}}\right] \frac{dV}{dx} . \tag{I.8.10}$$

If it is assumed that the conductance current of the membrane is a linear function of the membrane potential then

$$IR_M = V + R_M C_M \frac{\partial V}{\partial t} \tag{I.8.11}$$

and the combination of (I.8.10) and (I.8.11) is

$$\frac{\partial^2 V}{\partial Z^2} + K \frac{\partial V}{\partial Z} = V + \frac{\partial V}{\partial T} \tag{I.8.12}$$

where

$$K = \left(\frac{dZ}{dx}\right)^{-1} \frac{d}{dx} \ln\left(r^{\frac{3}{2}} n \left(\frac{ds}{dx}\right)^{\frac{1}{2}}\right) \tag{I.8.13}$$

and

$$T = \frac{t}{\tau} .$$

Hence, for a given K, the distribution of membrane potential over the dendrites is determined by equation (I.8.12) if, by (I.8.13), its branches satisfy

(I.8.14) $$\frac{n}{n_o} = \left(\frac{r}{r_o}\right)^{-\frac{3}{2}} \left(\frac{ds}{dx}\right)^{-\frac{1}{2}} e^{K(Z-Z_o)}$$

where n_o, r_o and Z_o are the values of n, r and Z for $x = 0$.

For the class of dendritic trees with $K = 0$, (I.8.12) reduces to cable equation (I.6.12) and the distribution of the membrane potential over the dendrites is equivalent to the distribution of the potential over a cylindrical core conductor whose length is expressed in units of Z . Furthermore, equations (I.8.6), (I.8.9) and (I.8.14) imply that in the case when $K = 0$, equal increments of dendritic surface area correspond to equal increments of length of the equivalent cylinder. This fact permits the comparison of the result of synaptic activity in distinct regions of the dendritic tree which have equivalent surface area but are at different distances x from the soma. If each branch of the tree is assumed to be a cylinder, that is, $\frac{ds}{dx} = 1$ in (I.8.6) then the class of dendritic trees with $K = 0$ can be extended to include dendritic trees with unequal branches at a given distance x from the soma. In this case the constraint on the branches at a given distance x from the soma is

(I.8.15) $$\sum_k \left(\frac{r_k}{r_o}\right)^{\frac{3}{2}} = 1$$

where r_k is the radius of the k^{th} branch and the summation over exhaust all branches at this value of x .

To determine the distribution of the membrane potential over a dendritic tree resulting from synaptic activity, it is necessary to consider both the effect of presynaptic activity on the membrane potential and the passive electrical properties of the membrane. Mathematically this is accomplished by combining (I.8.2) and (I.8.3), which account for the effect of presynaptic activity, with (I.8.12), which determines the passive distribution of the membrane potential over the dendritic tree. In the formulation, synaptic excitation and inhibition are assumed to be represented by step increases in G_ϵ and G_j , respectively. For the class of dendritic trees with $K = 0$, (I.8.2) and (I.8.12) can be combined to yield

$$\frac{\partial^2 V}{\partial Z^2} = k^2(V - V^*) + \frac{V}{T} . \tag{I.8.16}$$

To investigate the structural significance of the soma-dendritic region Rall (1962) considered two boundary valued problems for the system (I.8.16) and (I.8.3). The first corresponds to the decay from a nonuniform membrane potential distribution over the dendritic tree to a uniform steady state determined by the values chosen for k and V^* in (I.8.3). In this case the boundary conditions are

$$\left\{ \begin{array}{l} V(Z,0) = f(Z) \\ \text{and} \\ \dfrac{\partial V}{\partial Z} = 0 \quad \text{at} \quad Z = 0 \quad \text{and} \quad Z = L \end{array} \right. \tag{I.8.17}$$

where L is the length of the equivalent cylinder. The solution was obtained by the method of separation of variables together with an ordinary Fourier series expansion to satisfy the initial conditions. The second problem examines the resulting steady-state membrane potential distribution over the entire dendritic tree when initially the tree is separated into two distinct regions of uniform membrane potential distribution. On the equivalent cylinder of length $Z = 1$, the separated dendritic regions correspond to the lengths of cylinder from $Z = 0$ to $Z = A$, and from $Z = A$ to $Z = L$, respectively. Each length of the cylinder is represented by a distinct formulation of the system (I.8.16) and (I.8.3), defined by the regional values of k and V^* which are determined by values of G_ϵ, G_j and the membrane constants chosen to represent the region. The boundary condition in this case is

$$\text{(I.8.18)} \qquad \frac{\partial V}{\partial Z} = 0 \quad \text{at} \quad Z = 0 \quad \text{and} \quad Z = L$$

with both V and $\frac{\partial V}{\partial Z}$ assumed to be continuous at $Z = A$. The solution was obtained by the method of separation of variables together with a generalized Fourier series expansion. In both of the problems, the membrane potential across the soma was assumed to be the potential determined for the point $Z = 0$ on the equivalent cylinder.

The numerical results obtained by Rall (1962) to these two boundary value problems for a variety of initial conditions suggest there exists a functional distinction between dendritic and somatic symaptic activity. Dendritic synaptic activity, in particular, that

occurring at the dendritic periphery, seems to contribute significantly to the maintance and adjustment in the background level of membrane depolarization. Synaptic activity at or near the soma, however, seem to be effective in initiating precisely timed action potentials.

The applicability of this "equivalent-cylinder model" to the study of the dendritic trees is seriously restricted in two respects. First the constraint imposed by the power of $\frac{3}{2}$ in equation (I.8.15), although satisfied by the dendritic branches of motorneurons of the spinal cord, is not satisfied by the dendritic branches of all nerves. Secondly since a particular range of values of Z corresponds to a number of branches on the dendritic tree, it is impossible to consider the effect of synaptic activity which differs between branches that correspond to the same range of values of Z.

To overcome these difficulties, Rall (1964) proposed a "compartmental model" of the soma-dendritic region. In this model the dendritic tree is represented by a series of discrete elements or compartments.

Each isolated compartment was assumed to represent a uniform patch of soma-dendritic membrane. The mathematical formulation determining the membrane potential across such a uniform patch is given by (I.8.1). Hence for a given compartment, denoted by C_i, the membrane potential across the compartment satisfies the equivalent form of (I.8.1) given by

(I.8.19)
$$\frac{d\nu_i}{dt} = -\mu_i(\nu_i - \nu_{s_i})$$

where

(I.8.20)
$$\nu_i = \frac{E_{M_i} - E_r}{E_\epsilon - E_r}$$

$$\mu_i = \frac{1 + \mathcal{E}_i + \mathcal{J}_i}{\tau}$$

and

$$\nu_{s_i} = \frac{\mathcal{E}_i + \beta\mathcal{J}_i + \mathcal{X}_i}{1 + \mathcal{E}_i + \mathcal{J}_i}$$

for

(I.8.21)
$$\beta = \frac{E_j - E_r}{E_\epsilon - E_r}$$

$$\mathcal{E}_i = \frac{G_\epsilon}{G_r} = \frac{R_M}{R_\epsilon}$$

$$\mathcal{J}_i = \frac{G_j}{G_r} = \frac{R_M}{R_j}$$

and

$$\mathcal{X}_i = \frac{I_i R_M}{E_\epsilon - E_r} .$$

The notation of (I.8.19), (I.8.20) and (I.8.21) is defined as for equation (I.8.1) and those symbols which are not subscript with i are assumed to be the same for each compartment. The variable ν_i represents the normalized value of the departure of the membrane potential from the resting potential such that $\nu_i = 0$ when $E_{M_i} = E_r$ and

and $\nu_i = 1$ when $E_{M_i} = E_\epsilon$

For the case when two compartments are directly connected there will be a flow of current between them. If C_i and C_j denote two directly connected compartments then the net flow of current from C_j to C_i is

$$g_{ij}(\nu_j - \nu_i) \tag{I.8.22}$$

where g_{ij}, the conductance from C_j to C_i, is assumed to be equal to g_{ji}, the conductance from C_i to C_j. Hence, the membrane potential across compartment C_i when it is directly connected to another compartment, C_j, is determined by

$$\frac{d\nu_i}{dt} = (-\mu_i - \frac{g_{ij}}{c_i})\, \nu_i + \frac{g_{ij}}{c_i}\, \nu_j + \mu_i \nu_{s_i} \tag{I.8.23}$$

where c_i is the capacitance of C_i. By defining

$$\text{(I.8.24)} \quad \begin{cases} f_i = \mu_i \nu_{s_i} = \dfrac{E_i + \beta J_i + X_i}{\tau}, \\[2ex] \mu_{ij} = \dfrac{g_{ij}}{c_i}, \\[2ex] \text{and} \\[1ex] \mu_{ii} = -\mu_i - \dfrac{g_{ij}}{c_i} \end{cases}$$

then (I.8.23) is given by

(I.8.25) $$\frac{d\nu_i}{dt} = \mu_{ii}\nu_i + \mu_{ij}\nu_j + f_i \; .$$

For the general case consisting of n compartments the membrane potential across compartment C_i for $i = 1,2,3,\ldots,n$ satisfies

(I.8.26) $$\frac{d\nu_i}{dt} = \sum_{j=1}^{n} \mu_{ij}\nu_j + f_i ; \qquad i = 1,2,3,\ldots,n \; .$$

where

$$f_i = \frac{E_i + \beta J_i + X_i}{\tau}$$

(I.8.27) $$\mu_{ij} = \frac{g_{ij}}{c_i} = \frac{g_{ji}}{c_i} \quad \text{for} \quad i \neq j$$

$$\mu_{ij} = \frac{-(1 + E_i + J_i)}{\tau} - \sum_{j\neq i} \mu_{ij} \; .$$

and

(I.8.28) $$g_{ij} = g_{ji} = 0$$

for two compartments C_i and C_j which are not directly connected. Hence for the compartment model the distribution of the membrane potential over the soma-dendritic region is described by the system of linear first order differential equations (I.8.26).

The advantage of the compartmental model is that the region of the dendritic tree which each compartment represents is not specified and can be arbitrarily chosen according to the need of the problem.

Rall (1967) solved system (I.8.26) for a chain of ten compartments of which the first compartment C_1 was assumed to represent the soma. For each of the nine compartments associated with the dendrites, various values of G_ϵ and G_j were chosen and the potential change produced in C_1 was determined. Transient increases of G_ϵ in any compartment were assumed to be of the form

$$G_\epsilon t e^{1 - \frac{t}{\tau_d}} \qquad \text{(I.8.29)}$$

where τ_d is a constant. A number of predictions regarding the effect of the dendrite structure on processing of presynaptic stimulation were determined. Three of the more important predictions are that the same transients applied to compartments at increasing distance from the soma result in potentials at the soma of decreasing size and increased rise time, that small conductance changes are added linearly, and that time course changes of the conductance transients have greater effects at locations on the dendrites nearer the soma. The predictions have been tested with only partial success in the cat spinal mororneurons (Rall et al: 1967).

CHAPTER II

Introduction

The nerve impulse constitutes the output signal for the nerve. From microelectrode recordings it is observed that in a train of impulses, there is variability in the intervals between successive intervals. The activity of the nerve therefore has a stochastic nature in that it is impossible to predict the exact occurrence of an impulse (Johannesma: 1969). Hence, it is necessary to consider the activity of the nerve in probabilistic terms. The experimental data must therefore be analyzed in terms of certain statistical quantities such as the distribution of interresponse intervals.

The variability of the output signal is considered to import certain information regarding the generation of impulses. Mathematical models have therefore been developed which are capable of generating trains of impulse which resemble experimentally observed behavior. By analyzing such models it may be possible to determine the processes of the nerve which are responsible for such behavior.

As pointed out above, there is a random element associated with impulse generation. Experimental evidence exists which suggests, this randomness is inherent in the synaptic input to the nerve (Johannesma: 1969). It is therefore of interest to determine the output activity of a nerve in terms of the input signal characteristics. Such analysis results in an input-output relationship for nerve activity which

can be used as the basis for the interactions between nerves of a mathematical nerve network model. By analyzing the behavior of small nerve network models for which the activity of each nerve is determined by this input-output relationship it may be possible to gain insight into the activity of more realistic nerve networks.

§II.1 Random Walk Model of Neuronal Variability

As stated in the introduction to Chapter II, the variability in the spontaneous impulse pattern of a nerve may indicate certain properties of the mechanism of nerve impulse generation. In §I.1, an early attempt to derive a mathematical model which will generate the spontaneous activity of nerve is considered.

Rodieck, Kiang and Gerstein (1962) analyzed the spike train recordings of the spontaneous activity of a nerve in the cochlear nucleus of the cat. Three measurements were considered. These are the interresponse time, the joint distribution of two successive interresponse intervals, and the distribution of time intervals between 2^{m+1} action potentials, where m is a positive integer. For each measurement, a histogram was plotted. These histograms give an estimation of the probability density function for the respective distributions.

Two significant properties of the histograms enabled Gerstein and Mandelbrot (1964) to suggest a possible mathematical model for the generation of such spike train activity. First, the density function of the interresponse time distribution, must be able to account for comparatively long interresponse intervals. Furthermore, the data indicated for appropriate changes of the time scale, the histograms for the distribution of time intervals between 2^{m+1} action potentials for each m remains approximately the same as the histogram of the inter-

response time distribution. For this last property, if the duration of successive interresponse intervals is assumed independent, then successive convolutions of the density function for the interresponse time distribution, with itself, must remain of the same functional form, except for linear scaling changes of the independent variable. A probability distribution which satisfies this criterion is said to be stable.

A distribution whose density function satisfies both properties is that of the stable distribution of order $\frac{1}{2}$. This is, however, the probability density for the first passage time in a simple one-dimensional random walk which begins at a fixed distance from the absorbing barrier. Hence Gerstein and Mandelbrot (1964) considered the mathematical model which generates the spontaneous neural activity to be of that form.

The random walk model considered was given the following physiological interpretation. The membrane potential is represented by a state point on the one-dimensional x-axis. The threshold phenomena, corresponds to the absorbing barrier for the random walk, and is represented by the point $x = d$. If the membrane potential reaches the threshold value, $x = d$, and action potential is assumed to occur and the membrane potential is immediately reset to the resting value $x = x_o$. Steps taken during the random walk correspond to postsynaptic potentials resulting from presynaptic nerve impulses. An excitatory impulse produces a unit step toward the threshold, while an inhibitory impulse results in a unit step in the toward resting

potential.

By assuming the unit step sizes to be small in comparison to the difference $d - x_o$ and the temporal spacing between the incoming impulses to be small, it is possible in the limiting case to consider the random walk as a Wiener process (Cox and Miller: 1965). For this process, the stationary probability density function $f(y,t,x)$ that the membrane potential is at a value y at time t after the occurrence of a value x, assuming the value d has not been attained in the time interval, satisfies the forward diffusion equation

$$\frac{\partial f(y,t,x)}{\partial t} = - m \frac{\partial f(y,t,x)}{\partial y} + \frac{1}{2} s^2 \frac{\partial^2 f(y,t,x)}{\partial y^2} \tag{II.1.1.}$$

where m and s^2 are the mean and variance of the limiting process respectively. With the appropriate initial and boundary condition given by

$$f(y,0,x) = \delta(y - x_o)$$

$$\left.\begin{array}{l} f(-\infty,t,x) = 0 \\ \text{and} \\ f(d,t,x) = 0 \end{array}\right. \tag{II.1.2}$$

where $\delta = \delta(u)$ is the Dirac delta function; the solution (II.1.1) is

$$\text{(II.1.3)}\quad f(y,t,x) = \left[\frac{1}{s\sqrt{2t\pi}}\, e^{-\frac{1}{2}\left(\frac{y-x}{s\sqrt{t}}\right)^2} - \frac{1}{s\sqrt{2t\pi}}\, e^{-\frac{1}{2}\left(\frac{y-x-2d}{s\sqrt{t}}\right)^2} \right] e^{\frac{my-\frac{1}{2}m^2t}{s^2}} \qquad \text{for } t \geq 0$$

$$= 0 \quad \text{for } t < 0 .$$

The probability density function for the interresponse time distribution is given by the probability density $g(t,x_o)$ for the first passage time of the absorbing barrier starting from $x = x_o$. Using the property of conservation of probability given by

$$\text{(II.1.4)}\qquad g(t,x) = -\frac{\partial}{\partial t}\int_{-\infty}^{d} f(y,t,x)dy$$

and equation (II.1.1), $g(t,x_o)$ was determined to be

$$\text{(II.1.5)}\qquad g(t,x_o) = \frac{d-x_o}{t}\,\frac{1}{s\sqrt{2\pi t}}\, e^{-\frac{1}{2}\left(\frac{d-x_o-mt}{s\sqrt{t}}\right)^2} \qquad \text{for } t \geq 0$$

$$= 0 \quad \text{for } t < 0 .$$

Initially, Gerstein and Mandelbrot considered the average rate of incoming excitatory and inhibitory impulses to be equal. For this case, the probability of the occurrence of an excitatory impulse and the probability of the occurrence of an inhibitory impulse at time t are equal, and $m = 0$ in (II.1.5). Although for this case the stability property holds, the temporal scaling factor required to ensure stability

does not closely approximate that determined from the recorded data. If the rate of incoming excitatory and inhibitory impulses are assumed to be different, that is $m \neq 0$ in (II.1.5), then the stability property does not hold. However, for this case, an adequate approximation of the variance under convolution is obtained by judicious choice of the parameters.

In order to compare the theoretical predictions of the model with the experimental data, Gerstein and Mandelbrot considered $s^2 = 1$ and equation (II.1.5) to be of the generalized form

$$g(t,x_o) = Ke^{(-\frac{a}{t} - bt)} t^{-\frac{3}{2}} \tag{II.1.6}$$

where K is constant a is a constant representing the square of the distance between the threshold and reset value, and b is a constant denoting the difference in the rate of incoming excitatory and inhibitory impulses. For the appropriate choice of parameters it was possible to obtain a good fit with the experimentally determined histograms. Furthermore good agreement was found between the theoretical and experimental joint distribution of two successive interresponse intervals. Discrepancies in this case exist when the successive intervals are of a short duration. This was attributed to the fact that for the random walk model the duration of interspike intervals is independent while this was not the case for the experimental data.

Two major difficulties are inherent in the model. First it is impossible to obtain an exponential interresponse time distribution, which has been experimentally observed. Secondly, the large magnitude of the membrane time constant determined by the formulation has not been obtained experimentally for the vertebrate nervous system. Ten Hoopen (1966) suggests that this large value of membrane time constant can be attributed to the fact that each incoming impulse produces a postsynaptic potential which remains at a constant magnitude until it is abolished by an action potential. Both short comings of this random walk model have been overcome in the model proposed by Stein (1965), which is discussed in §II.2.

§II.2 Exponential Decay Model of Neuronal Variability

The model proposed by Gerstein and Mondelbrot (1964) to account for the variable spontaneous behavior of nerve was based predominately on the mathematical properties of the experimentally determined distribution of interresponse times for a single nerve type. Although the model is successful in reproducing the distributions on which it is based, it is not able to generate certain other experimentally recorded interresponse time distributions. To overcome these difficulties it is necessary to include in such a model certain of the experimentally determined properties of synaptic behavior in the nerve. In §II.2, a model of neuronal variability proposed by Stein (1965) which incorporates such behavior is discussed.

Experimental evidences indicate that postsynaptic potentials resulting from either excitatory or inhibitory presynaptic impulses can be summed, and decay approximately exponentially with time (Eccles: 1957). Furthermore, it was found that at certain synapses, in the absence of neural input, excitatory transmitter is released at random and the resulting postsynaptic potentials decay approximately exponentially (Katz and Miledi: 1963).

The model proposed by Stein (1965) incorporates these facts by assuming excitatory and inhibitory input impulses occur at random with mean frequencies n_e and n_i, respectively, and between impulses,

the depolarized subthreshold membrane potentials decays exponential with time constant τ . Each excitatory impulse was assumed to result in a unit depolarization while each inhibitory impulse produces c units repolarization. If the threshold value of membrane potential is reached an action potential is assumed to occur, where upon the membrane potential is immediately reset to the resting level.

With these assumptions the probability distribution $F(\nu,t)$ that the displacement V of the membrane potential from the resting potential is less than or equal to the value ν at time t satisfies

$$
\begin{aligned}
F(\nu,t+\Delta t) - F(\nu,t) = {} & [1-(n_e+n_i)\Delta t][F(\nu+\Delta\nu,t) - F(\nu,t)] \\
& - n_e\Delta t[F(\nu,t) - F(\nu-1,t)] + \\
& + n_i\Delta t[F(\nu+c,t) - F(\nu,t)]
\end{aligned}
\tag{II.2.1}
$$

and

$$1 - F(d,t+\Delta t) = 1 - F(d,t) + n_e\Delta t[F(d,t) - F(d-1,t)]$$

where d is the difference between the threshold potential and resting membrane potential, and $n_e\Delta t$ and $n_i\Delta t$ are the probabilities of the occurrence of an excitatory and an inhibitory presynaptic impulse, respectively, during the interval $(t,t+\Delta t)$. Since a depolarized subthreshold membrane potential decays exponentially toward the resting mambrane potential with time constant τ then

$$\frac{dV(t)}{dt} = -\frac{V(t)}{\tau} \tag{II.2.2}$$

and

(II.2.3) $$\Delta\nu = \frac{\nu}{\tau}\,\Delta t\ .$$

By (II.2.3), letting $\Delta t \to 0$ in (II.2.1) yields

(II.2.4) $$\frac{\partial F(\nu,t)}{\partial t} = \frac{\nu}{\tau}\frac{\partial F(\nu,t)}{\partial \nu} - n_e[F(\nu,t) - F(\nu - 1,t)] + n_i[F(\nu + c,t) - F(\nu,t)] \quad \text{for} \quad \nu < d$$

and

$$\frac{\partial F(d,t)}{\partial t} = - n_e[F(d,t) - F(d - 1,t)]\ .$$

The solution in (II.2.4) has not been obtained in a closed form. In order to investigate this formulation, two special cases of (II.2.4), which permit analytic treatment, have been considered. These cases result from assuming either that the action potential does not occur or that the decay of a depolarized subthreshold membrane potential is negligible.

By assuming the action potential does not occur, that is letting $d \to \infty$ in (II.2.4), reduces the formulation for $F(\nu,t)$ to

(II.2.5) $$\frac{\partial F(\nu,t)}{\partial t} = \frac{\nu}{\tau}\frac{\partial F(\nu,t)}{\partial \nu} - n_e[F(\nu,t) - F(\nu - 1,t)] + n_i[F(\nu + c,t) - F(\nu,t)] \quad \text{for} \quad \nu < \infty\ .$$

The solution to (II.2.5) is obtained by considering the transformed equation

(II.2.6) $$\frac{\partial C(p,t)}{\partial t} + - \frac{\partial C(p,t)}{\partial p} = n_e C(p,t)[1 - e^{ip}] - n_i C(p,t)[1 - e^{-iup}]$$

with boundary condition

$$C(p,t_o) = 1 \tag{II.2.7}$$

where

$$C(p,t) = \int_{-\infty}^{+\infty} e^{i\nu p} dF(\nu,t) \tag{II.2.8}$$

is the characteristic function for the distribution $F(\nu,t)$. Equation (II.2.6) can be reformulated into two ordinary linear differential equations for which the solution with boundary condition (II.2.7) is given by

$$\log C(p,t) = \int_{pe^{\frac{-(t-t_o)}{\tau}}}^{p} \left[- \frac{n_e(1 - e^{ix})}{x} - \frac{n_i(1 - e^{iux})}{x} \, dx \right] \tag{II.2.9}$$

or, equivalently

$$\log C(p,t) = \sum_{k=0}^{\infty} (ip)^k (1 - e^{-\frac{k}{\tau}(t-t_o)})(n_e\tau + n_i\tau(-u)^k) . \tag{II.2.10}$$

To examine the properties of this and the other special cases of (II.2.4) considered, Stein attempted to determine, where it is possible, the interresponse time distribution and mean frequency of response as a function of the input frequency. For the case in which the action potential is not assumed to occur, it is possible to examine the interresponse time distribution by determining the mean and variance of the membrane potential distribution $F(\nu,t)$. Since

$$\frac{\partial^n}{\partial ip^n} \log C(p,t)\Big|_{p=0} \tag{II.2.11}$$

is the nth cumulant of the distribution $F(\nu,t)$ then the mean μ_ν, and variance σ_ν^2 of the distribution $F(\nu,t)$ are

$$\mu_\nu = \frac{\partial}{\partial ip} \log C(p,t)\Big|_{p=0} = (n_e - cn_i)(1 - e^{-\frac{t-t_o}{\tau}}) \tag{II.2.12}$$

and

$$\sigma_\nu^2 = \frac{\partial^2}{\partial ip^2} \log C(p,t)\Big|_{p=0} = \frac{\tau}{2}\,(n_e + c^2 n_i)(1 - e^{-\frac{2}{\tau}(t-t_o)})\ . \tag{II.2.13}$$

Equations (II.2.10), (II.2.11) and (II.2.12) lead to two important conclusions with regard to the interresponse time distribution. By (II.2.10), as $t \to \infty$, the mean, variance and other cumulants of the distribution of the membrane potential with time approach steady state levels. The distribution of membrane potential, therefore, becomes time-dependent and for either weak excitation or predominant inhibition in which case the steady state mean membrane potential is always less than the threshold value, the conditional probability that an action potential occurs becomes constant for times greater than several time constants τ. Thus, the interresponse time distribution possesses an exponential tail. By (II.2.12) and (II.2.13), $\sigma_\nu^2(t)$ increases at a rate twice that of $\mu_\nu(t)$. Hence in the case of predominant inhibition for which $\mu_\nu(t) < 0$ in the steady state, the conditional probability that an action potential occurs can increase to significant values before attaining its constant value. The interresponse time distribution

in this case will rise to a sharp peak before approaching an exponential distribution.

For the special case of (II.2.4) in which the decay of a depolarized subthreshold membrane potential is assumed to be negligible Stein also assumed that the effect of excitation and inhibition are equal to one unit of depolarization and repolarization, respectively. The model therefore reduces to a birth and death process or queueing process with an absorbing barrier at $x = d$. In this case system (II.2.4) is replaced by

$$\left|\begin{array}{l} \dfrac{dF_k(t)}{dt} = n_e F_{k-1}(t) - (n_e + n_i) F_k(t) + n_i F_{k+1}(t) \quad \text{for} \quad 1<k<d-2 \\[2ex] \dfrac{dF_{d-1}(t)}{dt} = n_e F_{k-2}(t) - (n_e + n_i) F_d(t) \\[2ex] \dfrac{dF_d(t)}{dt} = n_e F_{d-1}(t) \\[2ex] \dfrac{dF_o(t)}{dt} = - n_e F_o(t) + n_i F_1(t) \end{array}\right. \tag{II.2.14}$$

where $F_k(t)$ is the probability that membrane potential is k units, for $k = 0,1,2,\ldots,d$, above the resting potential. The moments of the interresponse time distribution for this model have been determined by the method of probability generating functions. The mean interresponse time in this case is given by

$$(\text{II.2.15}) \quad \mu_t(t) = \frac{d-a}{n_e - n_i} + \frac{n_i}{(n_e - n_i)^2}\left[\left(\frac{n_i}{n_e}\right)^d - \left(\frac{n_i}{n_e}\right)^a\right] \quad \text{for} \quad n_i \neq n_e$$

$$= \frac{d - a(d + a - 1)}{2n_e} \quad \text{for} \quad n_i = n_e$$

where a is the initial displacement of the membrane potential from the resting potential (Bailey: 1964). Hence the mean frequency N of responses is

$$(\text{II.2.16}) \qquad N = \frac{1}{\mu_t(t)} = \frac{(n_e - n_i)^2}{(n_e - n_i)(d-a) + n_i\left[\left(\frac{n_i}{n_e}\right)^d - \left(\frac{n_i}{n_e}\right)^a\right]} \quad \text{for} \quad n_i \neq n_e \;.$$

By (II.2.16), for predominant excitation $n_e \gg n_i$ the frequency of responses is proportional to $n_e - n_i$, that is

$$(\text{II.2.17}) \qquad N = \frac{n_e - n_i}{d - a} \;,$$

and for predominant inhibition $n_i >> n_e$, N is a power function of n_e given by

$$(\text{II.2.18}) \qquad N = n_i\left(\frac{n_e}{n_i}\right)^d \;.$$

If, in addition to considering the decay of the subthreshold membrane potential to be negligible. It is also assumed that presynaptic inhibition is absent, then the model reduces to a Poisson process. Hence, the interresponse time distribution is a gamma distribution with the

probability density function $g(t)$ given by

$$g(t) = \frac{n_e^d (t - t_o)^{d-1} e^{-n_e(t-t_o)}}{(d - 1)!} \qquad t > t_o \tag{II.2.19}$$

$$= 0 \qquad t \leq t_o \; .$$

where t_o is the duration of the absolute refractory period following the action potential during which time incoming impulses are assumed to be ineffective. The mean μ_t and variance σ_t of the interresponse time distribution for (II.2.19) are

$$\mu_t = \frac{d}{n_e} + t_o \tag{II.2.20}$$

and

$$\sigma_t^2 = \frac{d}{n_e^2} \; . \tag{II.2.21}$$

Hence the mean frequency of responses is

$$N = \frac{1}{\mu_t} = \frac{\frac{n_e}{d}}{1 + \frac{t_o n_e}{d}} \; . \tag{II.2.22}$$

For the case in which potential decay is assumed to be negligible and inhibition to be absent, if d is less than or equal to one unit of depolarization then the interresponse time distribution is exponential. Hence, by considering the incoming impulses to be randomly distributed with time, overcomes one of the difficulties

present in the model proposed by Gerstein and Mandelbrot (1964).

The final special case for (II.2.4) considered by Stein assumes that potential decay and the threshold are present but that presynaptic inhibition is not. Solutions of the formulation in this case were obtained by computer simulation. for each choice of the parameters n_e, d and t_o considered in the simulations, it was possible to determine parameters n_e', d' and t_o' for a gamma distribution which would accurately approximate the simulated results.

To determine analytically the mean frequency of responses for this model it is necessary to reconsider equation (I.2.12) which determines the mean level of the membrane potential in the absence of the occurrence of an action potential. In the absence of presynaptic inhibition (II.2.23) reduces to

$$\mu_\nu(t) = n_e\tau(1 - e^{-\frac{t}{\tau}}) . \tag{II.2.24}$$

If it is assumed that the fractional variability $\frac{\sigma_\mu(t)}{\mu_\nu(t)}$ in the membrane potential is sufficiently small, then the mean time μ_t for the occurrence of an action potential would correspond to the time t after the refractory period t_o when the mean value of the membrane potential $\mu_\nu(t)$ is equal to the threshold. Hence by (II.2.23)

$$d = (n_e\tau)(1 - e^{\frac{-(\mu_t-t)}{\tau}}) \tag{II.2.25}$$

or equivalently

(II.2.26) $$\mu_t = -\tau \log \left(1 - \frac{d}{n_e\tau}\right) + t_o$$

in which case the mean frequency N of responses is given by

(II.2.27) $$N = \frac{1}{\mu_t} = \frac{1}{\tau \log\left[\frac{n_e\tau}{n_e\tau - d}\right] + t_o} .$$

Computer simulations were found to be in agreement with (II.2.26) if the parameters for the simulations were chosen such that $n_e\tau > 1.5d$.

The predictions of the model, proposed by Stein, and its special cases have been compared, where it is possible, with existing experimental results. Examples of the relation between N and n_e and n_i derived in equations (II.2.17), (II.2.18), and (II.2.22) have been obtained experimentally. The prediction of a gamma interresponse time distribution has been found for the interresponse time histograms for certain nerves. Furthermore, the interresponse time histograms of certain nerves revealed a sharp peak followed by a long tail as had be predicted in the case of predominant inhibition. In general, good comparison was found between the predictions and the experimental results.

For the model proposed by Stein (1965) the analytical predictions are restricted to the cases for which either the decay of the membrane potential between incoming impulses is negligible, or for which the action potential is assumed not to occur. Ten Hoopen (1966) attempted to design a model which would be more tractable than the

former, but would yield similar results in these limiting cases. The main difference between the two models was with regard to the decay of the subthreshold membrane potential between incoming impulses. For the model proposed by Stein, the effect of each depolarizing subthreshold input pulse is assumed to decay exponentially with time constant τ . In Ten Hoopen's model, the duration of the effect of each unit of subthreshold potential, resulting from an input impulse, is assumed to be exponentially distributed with mean τ .

In order to model the nerve when both excitatory and inhibitory incoming impulses are present, Ten Hoopen consider two cases. If the subthreshold membrane potential is depolarized at time t , then an excitatory impulse was assumed to result in a unit depolarization, while an inhibitory impulse returned the membrane potential one unit towards the resting potential. Further, the duration of each unit of depolarization resulting from an excitatory impulse was assumed to be exponentially distributed with mean τ . For a hyperpolarized somatic potential at time t , an inhibitory impulse further hyperpolarized the potential by one unit, while an excitatory impulse returned the potential one unit towards the resting value. The duration of each unit of hyperpolarization produced by an inhibitory impulse was also assumed to be distributed exponentially with mean τ . As in the case of the model proposed by Stein the arrival of excitatory and inhibitory impulses are each assumed to be distributed randomly with mean frequencies n_e and n_i , respectively. For this model the probability $F_k(t)$ the displacement V of the membrane potential from rest is equal to k at time t

after an action potential has occurred at $t = 0$ satisfies

(II.2.28)
$$F_k(t + \Delta t) = F_{k+1}(t)[1 - n_e\Delta t][n_i + \frac{k+1}{\tau}]\Delta t$$
$$+ F_k(t)[n_e\Delta t[n_i + \frac{k}{\tau}]\Delta t$$
$$+ F_k(t)[1 - n_e\Delta t][1 - n_i\Delta t - \frac{k}{\tau}\Delta t]$$
$$+ F_{k-1}(t)[n_e\Delta t][1 - n_i\Delta t - \frac{k-1}{\tau}\Delta t]$$

for $k = 1,2,\ldots,d-1$ where $F_{d+1}(t) = 0$,

(II.2.29)
$$F_k(t + \Delta t) = F_{k+1}(t)[n_i\Delta t][1 - n_e\Delta t - \frac{(- k - 1)}{\tau}\Delta t]$$
$$+ F_k(t)[n_i\delta t][n_e - \frac{k}{\tau}]\Delta t$$
$$+ F_k(t)[1 - n_i\Delta t][1 - n_e\Delta t - \frac{(-k)}{\tau}\Delta t]$$
$$+ F_{k-1}(t)[1 - n_i\Delta t][n_e - \frac{k - 1}{\tau}\Delta t]$$

for $k = -1,-2,-3,\ldots$, and

(II.2.30)
$$F_o(t + \Delta t) = F_1(t)[1 - n_e\Delta t][n_i + \frac{1}{\tau}]\Delta t$$
$$+ F_o(t)[1 - n_e\Delta t][1 - n_i\Delta t]$$
$$+ F_o(t)[n_i\Delta t][n_e\Delta t]$$
$$+ F_{-1}(t)[1 - n_i\Delta t][n_e + \frac{1}{\tau}]\Delta t$$

where $\frac{|k|}{\tau}\Delta t$ represents the probability of the membrane somatic potential returning one unit toward the resting potential during the interval $(t,t + \Delta t)$ when $V(t) = k$. Allowing $\Delta t \to 0$ then equations

(II.2.28), (II.2.29) and (II.2.30) yield

$$\text{(II.2.31)}\quad \frac{dF_k(t)}{dt} = (n_i + \frac{k+1}{\tau})F_{k+1}(t) - (n_i + \frac{k}{\tau} + n_e)F_k(t) + n_e F_{k-1}(t)$$

for $k = 1,2,\ldots,d-1$ and $F_{d+1}(t) = 0$

$$\text{(II.2.32)}\quad \frac{dF_k(t)}{dt} = n_i F_{k+1}(t) - (n_e - \frac{k}{\tau} + n_i)F_k(t) + (n_e - \frac{k-1}{\tau})F_{k-1}(t)$$

for $k = -1,-2,-3,\ldots$, and

$$\text{(II.2.33)}\quad \frac{dF_o(t)}{dt} = (n_i + \frac{1}{\tau})F_1(t) - (n_e + n_i)F_o(t) + (n_e + \frac{1}{\tau})F_{-1}(t)$$

respectively.

The probability density function $g(t)$ for interresponse time distribution is given by

$$\text{(II.2.34)}\qquad g(t) = n_e F_{d-1}(t) \ .$$

By introducing the reflecting barrier at $k = -r < 0$, for which

$$\text{(II.2.35)}\qquad \frac{d}{dt} F_{-r}(t) = n_e F_{-r+1}(t) - (n_e + \frac{r}{\tau} + n_i)F_{-r}(t) \ ,$$

and the initial conditions

$$\text{(II.2.36)}\qquad \begin{gathered} F_o(0) = 1 \\ \text{and} \\ F_k(0) = 0 \quad \text{for} \quad k = -r,-r+1,\ldots,-1,1,\ldots,d-1 \end{gathered}$$

then by solving the set of linear differential equations given by (II.2.31), (II.2.32) and (II.2.33) for $k = -r,\ldots,d-1$; and arbitrarily

close approximation of the solution of $F_{d-1}(t)$ and hence $g(t)$ can be determined.

A comparison with the results obtain for the model proposed by Stein was carried out for the limiting cases as either $\tau \to 0$ or $d \to \infty$. With the assumption that the action potential does not occur the mean value $\mu_\nu(t)$ of the membrane potential at time t was obtained using

(II.2.37)
$$\mu_\nu(t) = \sum_{k=-\infty}^{\infty} kF_k(t)$$

with initial condition

(II.2.38)
$$\mu_\nu(0) = 0 .$$

Hence $\mu_\nu(t)$ was determined to be

(II.2.39)
$$\mu_\nu(t) = \tau(n_e - n_i)(1 - e^{-\frac{t}{\tau}})$$

which corresponds to equation (II.2.12) for the exponential decay model of Stein with $c = 1$ and $t_o = 0$. For the case in which decay was neglected and $0 \leq k \leq d$ then the two models are both equivalent a queueing process with absorbing barrier at $k = d$.

If inhibition was neglected then the probability $F_k(t)$ that the $V(t) = k$ after an action potential occurs at $t = 0$, satisfies

$$\text{(II.2.40)} \qquad F_k(t + \Delta t) = F_{k+1}(t)[1 - n_e\Delta t][(k + 1)\frac{\Delta t}{\tau}]$$

$$+ F_k(t)[n_e\Delta t][k\,\frac{\Delta t}{\tau}]$$

$$+ F_k(t)[1 - n_e\Delta t][1 - k\,\frac{\Delta t}{\tau}]$$

$$+ F_{k-1}(t)[n_e\Delta t][1 - (k - 1)\,\frac{\Delta t}{\tau}]$$

for $k = 0,1,2,\ldots,d-1$ where

$$F_{-1}(t) = f_d(t) = 0 \ .$$

Allowing $\Delta t \to 0$, then (II.2.40) results in the set of linear differential equations

$$\text{(II.3.41)} \qquad \frac{dF'_k(t)}{dt} = (\frac{k + 1}{\tau})F_{k+1}(t) \ - (n_e + \frac{k}{\tau})F_k(t) + n_eF_{k-1}(t)$$

for $k = 0,1,2,\ldots,d-1$ where

$$F_{-1}(t) = F_d(t) = 0 \ .$$

With the initial conditions

$$\text{(II.2.42)} \qquad \begin{cases} F_o(0) = 1 \\ \text{and} \\ F_k(0) = 0 \quad \text{for} \quad k = 1,2,3,\ldots,d-1 \end{cases}$$

then an exact solution can be obtained for the set of first order linear differential equations (II.2.41) and for $g(t) = n_eF_{d-1}(t)$, the density function for the interresponse time distribution.

In order to compare the models of Stein and Ten Hoopen when only excitation was present, the limiting cases were again considered. If the decay between impulses is negligible, the two models are equivalent to a Poisson process and therefore yield a gamma interresponse time distribution. For the case in which the action potential was assumed not to occur then the mean value $\mu_\nu(t)$ of the membrane potential at time t for the exponentially distributed decay model of Ten Hoopen was determined to be

$$\text{(II.2.43)} \qquad \mu_\nu(t) = n_e\tau(1 - e^{-\frac{t}{\tau}}) .$$

The same value was obtained for the exponential decay model under these conditions. The variance $\sigma_\nu^2(t)$ of the membrane potential at time t for the exponentially distributed decay model was determined to be

$$\text{(II.2.44)} \qquad \sigma_\nu^2(t) = n_e\tau(1 - e^{-\frac{t}{\tau}}) .$$

Equation (II.2.44) can be put in the equivalent form

$$\text{(II.2.45)} \qquad \sigma_\nu^2(t) = \frac{2(1 - e^{-\frac{t}{\tau}})}{1 - e^{-\frac{2t}{\tau}}} \frac{n_e\tau}{2} (1 - e^{-\frac{2t}{\tau}})$$

for comparison with $\sigma_\nu^2(t)$ given by equation (II.2.13) for the model proposed by Stein in the case when $n_i = 0$ and $t_o = 0$. Since

(II.2.46) $$1 \leq 2 \frac{(1 - e^{-\frac{t}{\tau}})}{1 - e^{\frac{2t}{\tau}}} \leq 2$$

then the variance in the exponentially distributed decay model is at the most twice that in the case of Stein's model. This implies the mean interresponse interval is shorter in the case of the exponentially distributed decay model if the threshold is reintroduced.

To consider the effect of this descrepancy the threshold and decay were reintroduced into both models. For the case in which only excitation was present, Stein had obtained computer simulations for the interresponse time distribution. In each case the distribution can be closely approximated by a gamma distribution. Close agreement between the mean and variance of these gamma distributions and the mean and variance determined by Ten Hoopen's model under these conditions was obtained if the input frequencies were corrected by a factor for exponentially distributed decay model.

Thus the two models are in close agreement and the exponentially distributed model with its advantage of an analytical approach becomes a useful reference for the more realistic exponential decay model.

In addition to being an approximation of the exponential decay model, Ten Hoopen's model has further applications. Ten Hoopen

suggested that the exponentially distributed decay model may be applicable for modelling the variable duration of post-synaptic potentials of incoming impulses resulting from the transmission properties of the synaps or the distance between the synaps and the soma. Furthermore, it was pointed out that nonlinear summation can conveniently be incorporated in the model.

In §II.1 and §II.2 three models have been presented which attempt to account for the variability in the interresponse interval. In §I.1 through §I.4 a variety of mathematical models for nerve excitation were considered. For these excitation models it was possible to determine a general formulation for which each of the models is a special case. This is also the case for the models of neuronal variability discussed in §II.1 and §II.2. The generalization will be discussed in §II.3.

§II.3 Generalized Mathematical Model for Neuronal Variability

For the models discussed in §II.1 and §II.2, the variability in the interresponse intervals is attributed to the fluctuations in synaptic input. Therefore, in order to determine the mathematical description of the signal processing aspect of neural activities it is necessary to account not only for the properties of the nerve but also the properties of the input signal. Johannesma (1969) has presented a formal mathematical treatment of signal processing which is based on five fundamental assumptions determined both by the nerve properties and the input signal characteristics. The resulting formulation for the subthreshold behavior of the nerve to synaptic input proves to be the general case for which the models discussed in §I.1 and §I.2 are special cases.

The first assumption is that for the nerve the subthreshold potential behavior is completely described by the single variable V, which measures the displacement of the membrane potential from the resting membrane potential, and for which the rate of change at time t is dependent only on the value of V at time t and the influence $i(t)$, of other neurons at time t. This dependence is described by

$$\frac{dV}{dt} = f(V) + g(V) \cdot i(t) \tag{II.3.1}$$

where f and g are differential functions.

The input signal $i(t)$ represents the membrane current resulting from changes in synaptic permeability. Since a nerve may receive synaptic input from a large number of other nerves the detailed structure of $i(t)$ may be very complex. To reduce the difficulties of attempting to describe all the complexities of such input, $i(t)$ is regarded as a stochastic process which can be characterized by its most prominent features, the mean

$$m(t) = \langle i(t) \rangle \tag{II.3.2}$$

and incremental variance

$$s^2(t) = \int_{-\infty}^{+\infty} \langle i(t)\cdot i(t-\tau) \rangle - \langle i(t) \rangle \langle i(t-\tau) \rangle \, d\tau \quad . \tag{II.3.3}$$

To normalize this input signal to one of zero mean and unit variance, $i(t)$ is considered to be of the form

$$i(t) = m(t) + s(t) \cdot j(t) \tag{II.3.4}$$

where

$$j(t) = \frac{i(t) - m(t)}{s(t)} \quad . \tag{II.3.5}$$

Hence (II.3.1) is transformed to

$$\frac{dV}{dt} = \alpha(V,t) + \ (V,t) \cdot j(t) \tag{II.3.6}$$

where

$$\alpha(V,t) = f(V) + g(V) \cdot m(t)$$

(II.3.7) and

$$\beta(V,t) = g(V) \cdot s(t) \quad .$$

In (II.3.6) and (II.3.7) the properties of the nerve are determined by $f(V)$ and $g(V)$ and the characteristics of the input are determined by $m(t)$ and $s(t)$. The explicit behavior of $j(t)$ is unknown and it may under certain circumstances be considered as a stochastic carrier for which its microscopical properties are irrelevant to the behavior of system (II.3.6) and (II.3.7). In order to determine the conditions under which this interpretation of $j(t)$ is valid it is necessary to consider three time constants which are related to the system (II.3.6) and (II.3.7). These are the time constant τ_c of the statistical fluctuations of the input defined by

$$\text{(II.3.8)} \qquad \tau_c = \frac{1}{s^2(t)} \int_{-\infty}^{\infty} \frac{\tau}{\langle i(t)\cdot i(t-\tau)\rangle - \langle i(t)\rangle\langle i(t-\tau)\rangle} \, d\tau \ ,$$

the time constant τ_s of the variation of the statistical characteristics of the input defined by

$$\text{(II.3.9)} \qquad \tau_s = \left| \left\{ \frac{\frac{d}{dt} m(t)}{m(t)} \right\}^2 + \left\{ \frac{\frac{d}{dt} s(t)}{s(t)} \right\}^2 \right|^{\frac{1}{2}}$$

and the time constant τ_r for the relaxation of the system defined by

$$\text{(II.3.10)} \qquad \tau_r = -\left\langle \left| \frac{\partial}{\partial y} \ (y,t) + (y,t) j(t) \right|^{-1} \right\rangle \ .$$

The second fundamental assumption of Johannesma's treatment requires that

$$\text{(II.3.11)} \qquad \left\{ \begin{array}{l} \tau_c << \tau_s \\ \text{and} \\ \tau_c << \tau_r \ . \end{array} \right.$$

By this assumption, for time differences Δt , such that $\tau_r = \tau_c$, the microscopical properties of $j(t)$ are irrelevant to the behavior of system (II.3.6) and (II.3.7) and $j(t)$ may be replaced by the white noise signal $\omega(t)$ which has zero mean, unit variance, and a delta correlation function. Equation (II.3.6) is in this case replaced by the Langevin equation

$$dV = \alpha(V,t)dt + \beta(V,t)dW(t) \tag{II.3.12}$$

where

$$\frac{dW(t)}{dt} = (t)$$

$$\langle \omega(t) \rangle = 0 \tag{II.3.13}$$

and

$$\langle \omega(t) \cdot \omega(t+\tau) \rangle = \delta(\tau) \ .$$

Thus the replacement of $j(t)$ by $\omega(t)$ implies that for $\Delta t >> \tau_c$ the process described by (II.3.6) is a first order Markov process described by (II.3.12).

In order to analyze (II.3.12) it is necessary to consider the transition probability density function $f(y,t|x,s)$ the probability density that V has a value y at time t given that it was x at time s . The fact $\omega(t)$ has a delta correlation function, implies that the transition probability density is independent of previous history. Hence $f(y,t|x,s)$ satisfies the Smoluchowski equation

(II.3.14)
$$f(y,t + \Delta t|x,s) = \int f(y,t + \Delta t|z,t)f(z,t|x,s)dz$$

or equivalently

(II.3.15)
$$\frac{\partial}{\partial t} f(y,t\ x,s) = \sum_{n=1}^{\infty} \frac{(-1)^n}{n!} \frac{\partial^n}{\partial y^n} \{A_n(y,t)f(y,t|x,s)\}$$

where

(II.3.16)
$$A_n(y,t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int z^n f(y + z,\ t + \Delta t|y,t)dz$$

are the incremental moments of which the first two, the drift of V

(II.3.17)
$$A_1(y,t) = a(y,t)$$

and dispersion of V

(II.3.18)
$$A_2(y,t) = b(y,t)$$

are the most significant.

It is possible to simplify the Smoluchowski differential equation to a second order partial differential equation. In order to do this it is necessary to consider the amplitude distribution of the white noise $\omega(t)$. If the amplitude distribution of $\omega(t)$ is assumed to be Gaussian then $\omega(t)$ is continuous and (II.3.12) describes a continuous first order Markov process. In this case

(II.3.19)
$$A_n(y,t) = 0 \quad \text{for} \quad n \geq 3$$

in (II.3.15). Hence the third fundamental assumption of Johannesma's model is that $\omega(t)$ is continuous. The consequence of this third assumption is that (II.3.15) reduces to the forward differential equation

$$(\text{II}.3.20)\qquad \frac{\partial}{\partial t} f(y,t|x,s) = -\frac{\partial}{\partial y}\{a(y,t)f(y,t|x,s)\} + \frac{\partial^2}{\partial y^2}\{\tfrac{1}{2}\, b(y,t)f(y,t|x,s)\}$$

where $a(y,t) = A_1(y,t)$ is the drift of V and $b(y,t) = A_2(y,t)$ is the dispersion of V. Furthermore $f(y,t|x,s)$ also satisfies the backward diffusion equation

$$(\text{II}.3.21)\qquad \frac{\partial}{\partial s} f(y,t|x,s) = a(x,s)\frac{\partial}{\partial x} f(y,t|x,s) + \frac{1}{2}\, b(x,s)\frac{\partial^2}{\partial y^2} f(y,t|x,s)\ .$$

It has been demonstrated that the drift and dispersion terms of the diffusion equations (II.3.20) and (II.3.21) are related to the signal characteristics α and β of the fluctuation equation (II.3.12) (Stratonovich: 1963). The relationship is given by

$$(\text{II}.3.22)\qquad \left\{\begin{array}{l} a(y,t) = \alpha(y,t) + \dfrac{1}{4}\dfrac{\partial}{\partial y}\{\beta(y,t)\}^2 \\ \text{and} \\ b(y,t) = \{\beta(y,t)\}^2\ . \end{array}\right.$$

For the stationary case, in which the mean and variance of the input are independent of time, the transition probability density is $f(y,t,x)$, the probability density of the transition of V from x to y in a time interval of duration t. Diffusion equations (II.3.20) and (II.3.21) in the stationary case are replaced by

$$(\text{II}.2.23)\qquad \frac{\partial}{\partial t} f(y,t,x) = -\frac{\partial}{\partial y}\{a(y)f(y,t,x)\} + \frac{\partial^2}{\partial y^2}\{\tfrac{1}{2}\, b(y)f(y,t,x)\}$$

and

$$\text{(II.3.24)} \quad \frac{\partial}{\partial t} f(y,t,x) = a(x)\frac{\partial}{\partial x} f(y,t,x) + \frac{1}{2} b(x)\frac{\partial^2}{\partial x^2} f(y,t,x) \ ,$$

respectively.

In order to complete the diffusion equations for the stationary case it is necessary to define the initial and boundary conditions. For the forward diffusion equation (II.3.23), the obvious initial and boundary condition which hold are

$$\text{(I.3.25)} \quad \begin{array}{c} f(y,0,x) = (y - x) \\ \text{and} \\ f(-\infty,t,x) = 0 \ . \end{array}$$

To obtain a second boundary condition an assumption is required. This fourth fundamental assumption of the formulation establishes the existence of a threshold value of the membrane potential for the initiation of an action potential. The boundary condition for (II.2.23) resulting from the assumption is

$$\text{(II.3.26)} \quad f(d,t,x) = 0$$

where d is the difference between the threshold potential and the resting membrane potential. This assumption also places a restriction on the transition probability density function $f(y,t,x)$. The function $f(y,t,x)$ is redefined to be the probability density that V moves from x to y in the time interval t, assuming that V has not attained the value d.

The fifth fundamental assumption is included in the formulation

to simplify the mathematical description of repetitive activity. This is accomplished by ommitting all refractory properties of the action potential by assuming that V is returned to a reset value x_o immediately upon the initiation of an action potential.

With these assumptions and formulation Johannesma was able to show that the formulations for the subthreshold behavior of each of the models discussed in §II.1 and §II.2 are special cases of the Smoluchowski differential equations (II.3.15) for the stationary case given by

$$\frac{\partial}{\partial t} f(y,t,x) = \sum_{n=1}^{\infty} \frac{(-1)^n}{n!} \left(\frac{\partial}{\partial y}\right)^n A_n(y) f(y,t,x) \tag{II.3.27}$$

where $A_n(y)$ is defined by (II.3.16). The mathematical differences between the models is expressed in their formulations for the incremental moments $A_n(y)$. For the five basic assumptions only the third, $\omega(t)$ is continuous, is not satisfied by each of the models. The models which do not satisfy this third assumption are the exponential decay model of Stein (1965) and the exponentially distributed decay model of Ten Hoopen (1966). In both cases the input signal was assumed to be discrete in nature.

For the model proposed by Gerstein and Mandelbrot (1964) discussed in §II.1, equation (II.3.1) is given by

$$\frac{dV}{dt} = i(t) \; . \tag{II.3.28}$$

Hence by (II.3.7), (II.3.19), (II.3.22), and (II.3.28) the incremental moments are given by

$$\text{(II.3.29)}\qquad \begin{cases} A_1(y) = a(y) = m \\ A_2(y) = b(y) = s^2 \\ \text{and} \\ A_j(y) = 0 \quad \text{for} \quad j \geq 3 \end{cases}$$

where m and s^2 are defined by (II.3.2) and (II.3.3). Thus the sub-threshold behavior as determined by the model of Gerstein and Mandelbrot is described by the Smoluchowski equation

$$\text{(II.3.30)}\qquad \frac{\partial}{\partial t} f(x,t,y) = \frac{\partial}{\partial y}\{mf(x,t,y)\} + \frac{1}{2}\frac{\partial^2}{\partial y^2}\{s^2 f(x,t,y)\}$$

which is equivalent to (II.1.1) of the formulation proposed by Gerstein and Mandelbrot.

In order to examine the models of Stein (1965) and Ten Hoopen (1966) in terms of the generalized formulation it is necessary to derive expressions for the input when it is of a discrete nature. The formulation determined for the stationary discrete input $i(t)$ is

$$\text{(II.3.31)}\qquad i(t) = m + s\omega(t)$$

where

$$\text{(II.3.32)}\qquad m = \sum_k n_k c_k$$

and

$$\text{(II.3.33)}\qquad s^2 = \sum_k n_k c_k$$

n_k is the frequency of arrival of presynaptic nerve impulses at the k^{th} synaps, and c_k is the modality and strength of the effect of the impulse at the k^{th} synaps.

For the exponential decay model proposed by Stein, equation (II.3.1) is given by

$$\frac{dV}{dt} = -\frac{V}{\tau} + i(t) \; . \tag{II.3.34}$$

From (II.3.7), (II.3.16), (II.3.31) and (II.3.34) the incremental moments are

$$\left\{\begin{array}{l} A_1(y) = a(y) = m - \frac{y}{\tau} \\ A_2(y) = b(y) = s^2 \\ \text{and} \\ A_j(y) = \sum\limits_k n_k c_k^j \quad \text{for} \quad j \geq 3 \end{array}\right. \tag{II.3.35}$$

where m and s^2 are given by (II.3.32) and (II.3.33). Hence the resulting Smoluchowski equation is

$$\frac{\partial}{\partial t} f(y,t,x) = \frac{\partial}{\partial y} \frac{y}{\tau} \{f(y,t,x)\} + \sum_k n_k \{f(y-c_k,t,x) - f(y,t,x)\} \tag{II.3.36}$$

for which the integrated version is given by (II.2.5) in the formulation derived by Stein.

In the case of Ten Hoopen's model for which the decay of the membrane potential occurs in jumps with the probability of occurrence exponentially distributed, only the special case where all excitatory

and inhibitory input impulses are of equal strength was consider. Hence

(II.3.37) $$c_k = \pm c$$

in (II.3.32) and (II.3.33). The incremental moments in this case are given by

(II.3.38) $$A_j(y) = n_e c^j + n_i(-c)^j - (-c)^{j-1} \frac{y}{\tau}$$

for $y > 0$ and $j = 1,2,3,\ldots$ where n_e and n_i are the frequency of the excitatory and imhibitory impulses, respectively. The Smoluchowski equation for $y > 0$ is

(II.3.39) $$\begin{aligned}\frac{\partial}{\partial t} f(y,t,x) = {} & \frac{1}{c\tau} (y + c)f(y + c,t,x) - yf(y,t,x) \\ & + n_e\{f(y - c,t,x) - f(y,t,x)\} \\ & + n_i\{f(y + c,t,x) - f(y,t,x)\} .\end{aligned}$$

for which the integrated forms is given by (II.2.34) of Ten Hoopen's formulation. For the cases in which $y = 0$ and $y > 0$ analogous Smoluchowski equations apply.

An extension of the model proposed by Gerstein and Mandelbrot (1964) was also considered by Johannesma. This model, which had first been proposed by Gluss (1967), resulted by including in the model of Gerstein and Mandelbrot (1964) the proposal that subthreshold membrane potentials decay exponentially with time towards the resting membrane potential. In this case the general equation (II.3.1) is of the form

(II.3.40) $$\frac{dV}{dt} = - \frac{V}{\tau} + i(t) .$$

Since the model also satisfies the other four assumptions of the general formulation then by (II.3.7), (II.3.16), (II.3.22) and (II.3.40) the incremental moments are

$$A_1(y) = a(y) = m - \frac{y}{\tau}$$

$$A_2(y) = b(y) = s^2 \tag{II.3.41}$$

and

$$A_j(y) = 0 \quad \text{for} \quad j \geq 3 \ .$$

Thus the Smoluchowski equation determining the subthreshold behavior is

$$\frac{\partial}{\partial t} f(y,t,x) = -\frac{\partial}{\partial y}\{(m - \frac{y}{\tau})f(y,t,x)\} + \frac{1}{2}\frac{\partial^2}{\partial y^2}\{s^2 f(y,t,x)\} \tag{II.3.42}$$

where m and s are given by (II.3.2) and (II.3.3).

Having established a generalized model for neuronal variability based on both the properties of the nerve and the characteristics of the input signal, it is now of interest to determine its behavior in terms of the input characteristics. In §II.4, the stationary activity of two special cases of the Johannesma's formulation will be discussed.

§II.4 Stationary Behavior of the Perfect Integrator and Leaky Integrator

In order to be able to examine a mathematical model for the signal processing activity of the nerve it is necessary to formulate in terms of the model, statistical measurements of nerve behavior which are amenable to experimental investigation. Such measurements include the distribution of interresponse time, the distribution of membrane potential, and the mean interresponse interval. To determine the behavior of the general formulation proposed by Johannesma for signal processing models, Johannesma (1969) analyzed the stationary activity of two special cases of this general formulation. These are the model proposed by Gerstein and Mandelbrot (1964) described by (II.3.28), (II.3.29) and (II.3.30) and its extension, the model proposed by Gluss (1967) discribed by (II.3.40), (II.3.41) and (II.3.42). The models are referred to respectively as the Perfect Integrator and Leaky Integrator, a nomenclature which in each case describes the membrane's effect on subthreshold inputs. For each model it is possible to obtain certain general conclusions regarding the behavior of the model in terms of the input characteristics.

To determine the required statistical measurements, it was necessary to consider three probability density functions in addition to $f(y,t,x)$, defined in §II.3. These are the probability density $g(t,x)$ that the first action potential occurs at time t after $V = x$, the probability density $h(y,t,x)$ that V is at a value y at time t

after the occurrence of the value x irrespective of whether an action potential has occurred in the time interval, and the probability density $n(t,x)$ that an action potential occurs at time t after $V = x$. Two important special cases of these functions are $g(t,x_o)$ and $n(t,x_o)$ where x_o is the reset value taken by V immediately after an action potential occurs. $g(t,x_o)$ is the probability density for the interval between action potentials, while $n(t,x_o)$ is the conditional event density that an action potential occurs at time t after the occurrence of an action potential.

Using these probability density functions, Johannesma was able to derive general expressions for the stationary distribution of the membrane potential and the moments of the interresponse time distribution in terms of the coefficients $a(y)$ and $b(y)$ of the diffusion equation (II.3.23). The stationary probability density $h(y)$ for the membrane potential was determined to be

$$\text{(II.4.1)} \quad h(y) = \lim_{t\to\infty} h(y,t) = T_1^{-1}(x_o)\,\frac{e^{C(y)}}{\frac{1}{2}\,b(y)} \int_y^d \varepsilon(z - x_o)e^{-C(z)}dz$$

where

$$c(y) = \frac{a(y)}{\frac{1}{2}\,b(y)} \quad ,$$

(II.4.4)

$$C(y) = \int^y c(z)dz \ ,$$

$\varepsilon(z - x_o)$ is the Heaveside unit function and $T_1(x_o)$ is the mean interresponse time. Using (II.3.22), an equivalent formulation for $h(y)$ can be obtained in terms of the coefficients, $\alpha(y)$ and $\beta(y)$ of the fluctuation equation (II.3.12). In this case

$$h(y) = T_1^{-1}(x_o) 2 \frac{e^{\Gamma(y)}}{\beta(y)} \int_y^d \varepsilon(z - x_o) \frac{e^{-\Gamma(z)}}{(z)} dz \tag{II.4.3}$$

where

$$\left\{ \begin{aligned} \gamma(y) &= \frac{\alpha(y)}{\frac{1}{2}\beta^2(y)} \\ &\text{and} \\ \Gamma(y) &= \int^y \gamma(z) dz \quad . \end{aligned} \right. \tag{II.4.4}$$

In order to determine the distribution of the interresponse times it is necessary to determine the probability density $g(t,x_o)$. By the backward diffusion equation (II.3.24) and the property of conservation of probability given by

$$g(t,x) = -\frac{\partial}{\partial t} \int_{-\infty}^d f(y,t,x) dy \tag{II.4.5}$$

$g(t,x)$ satisfies

$$\frac{\partial}{\partial t} g(t,x) = a(x) \frac{\partial}{\partial x} g(t,x) + \frac{1}{2} b(x) \frac{\partial^2}{\partial x^2} g(t,x) \tag{II.4.6}$$

with initial and boundary conditions

$$g(0,x) = 0$$

$$g(t,x) = \delta(t)$$

(II.4.7) and

$$\lim_{x \to -\infty} g(t,x) = 0 \ .$$

The solution of (II.4.6), with initial and boundary conditions (II.4.7), exists in closed form only for the cases in which the coefficients $a(x)$ and $b(x)$ are independent of x. Therefore, to be able to characterize the interresponse time distribution when the coefficients of (II.4.6) are not constant, Johannesma determined expressions for the moments $T_n(x)$ of the interresponse time distribution. The formulation obtained is

$$T_n(x) = n!2 \int_x^d \frac{e^{-\Gamma(y)}}{\beta(y)} \int_{-\infty}^y \frac{e^{\Gamma(z)}}{\beta(z)} \, dz \, dy \qquad n = 0,1,2,3, \tag{II.4.8}$$

where Γ and β are given in (II.4.4). Since formulations (II.4.1), for the stationary distribution of the membrane potential, and (II.4.8), for the moments of the interresponse time distribution, are derived in terms of the coefficients of the fluctuation equation (II.3.12) and diffusion equation (II.3.23), both expressions can be applied to the two models under consideration.

For the Perfect Integrator model, the probability density $g(t,x_o)$ for the interval between responses can be determined explicitly since the coefficients $a(x)$ and $b(x)$ of (II.4.6) are equal to the constants m and s^2, respectively. The interresponse time distribution is therefore

(II.4.9) $$g(t,x_o) = \frac{d - x_o}{t} \frac{1}{s\sqrt{2\pi t}} e^{-\frac{1}{2}\left(\frac{d-x_o-mt}{s\sqrt{t}}\right)^2}$$

The mean interresponse time $T_1(x_o)$ for the Perfect Integrator is obtained by solving (II.4.8) for $\alpha(y) = m$, $\beta(y) = s$, and $n = 1$. Hence

(II.4.9) $$T_1(x_o) = \frac{d - x_o}{m}$$

and the mean frequency of response N is

(II.4.10) $$N = \frac{1}{T_1(x_o)} = \frac{m}{d - x_o} .$$

Solving (II.4.3) and (II.4.4) with $\alpha(y) = m$ and $\beta(y) = s$, as defined in the case of the Perfect Integrator, yields

$$h(y) = \frac{1}{d - x_o} \{e^{c(y-x_o)} - e^{c(y-d)} + \varepsilon(y - x_o)[1 - e^{c(y-x_o)}]\}$$

(I.4.11) with

$$c = \frac{m}{\frac{1}{2} s^2} .$$

for the stationary probability density of the membrane potential. From (II.4.11), Johannesma concluded that, for the Perfect Integrator, the stationary distribution of the membrane potential depends on the ratio of the mean and incremental variance of the input signal rather than their individual values.

In the case of the Leaky Integrator a closed solution to (II.4.6), which determines the distribution of interresponse times, can

not be obtained since coefficient $a(x)$ given by

$$a(x) = m - \frac{x}{\tau} \tag{II.4.12}$$

for the Leaky Integrator model, is not independent of x. However, the moments of the interresponse time distribution can be determined by (II.4.8), with the appropriate substitutions for α and β. The resulting formulation is

$$\frac{T_n(x)}{n!} = \tau \frac{2}{\tau s^2} \int_x^a e^{\frac{(y-m\tau)^2}{s^2\tau}} \left[\int_\infty^y e^{-\frac{(z-m\tau)^2}{s^2\tau}} \frac{T_{n-1}(z)}{(n-1)!} \, dz \right] dy \, . \tag{II.4.13}$$

(II.4.13) can be simplified by introducing the dimensionless variables

$$\left\{ \begin{aligned} X &= \frac{m\tau - x}{s\tau} \, , \\ D &= \frac{m\tau - d}{s\tau} \, , \\ \text{and} \quad \mu_n &= \frac{1}{n!} \frac{T_n(x)}{\tau^n} \, . \end{aligned} \right. \tag{II.4.14}$$

The result is a recurrence relationship given by

$$\mu_n(X,D) = 2\int_D^X e^{y^2} \left[\int_y^\infty e^{-z^2} \mu_{n-1}(z,D)\,dz \right] dy \, . \tag{II.4.15}$$

From (II.4.15), Johannesma concluded that if time is measured in units of the time constant, then the moments of the interval distribution for a Leaky Integrator depend only on the two combinations of system and input parameters given by X and D. For the mean interresponse time

$T_1(x)$ numerical computations were made. The result were formulated in terms of three dimensionless variables. These are $N = \frac{\tau}{T_1}$, the average number of responses within a time constant, $M = \frac{m}{d}$, the steady state value of the somatic potential in the absence of a threshold, and $S^2 = \frac{s^2\tau}{d}$. By curve fitting, the relationship, in terms of these dimensionless variables, between the mean interresponse time $T_1(x)$ and the mean m and incremental variance s of the input was determined to be most accurately approximated by

$$N = e^{\alpha M+\beta S^2-\alpha N-\delta} \tag{II.4.16}$$

where α, β, and δ are constant. The stationary distribution $h(y)$ of the membrane potential for a Leaky Integrator was also determined. By (II.4.3) the formulation is

$$h(y) = \frac{2}{s^2 T_1} e^{-\left(\frac{y-m\tau}{s^2\tau}\right)} \int_y^d \varepsilon(z - x_o) e^{\left(\frac{z-m\tau}{s^2\tau}\right)^2} dz . \tag{II.4.17}$$

Thus it is possible to describe stationary behavior of the Perfect Integrator and Leaky Integrator models in terms of the input signal characteristics. Of interest is the relationship determined between the mean interresponse time and the input signal characteristics for the Leaky Integrator model. This relationship, defined by (II.4.16) is essentially an input-output relationship for the nerve and as such will form the basis of the interaction equation for a nerve net model described in §II.5.

§II.5 Mathematical Model of a Nerve Network

In the Introduction of Chapter II it was suggested that it is possible to derive a mathematical model for a nerve network in terms of the interactions between the individual members of the network. In order to do this it must be possible to define the activity of each nerve in terms of its input signal characteristics. Therefore, a natural starting point for the mathematical formulation is the input-output relationship given by (II.4.16) which was derived for the Leaky Integrator Model. Since this equation would describe the behavior of a single member of the network, it is subscripted to distinguish the nerves of the net. Hence (II.4.16) is

$$N_i = e^{\{\alpha_i M_i + \beta_i S_i^2 - \alpha_i N_i - \delta_i\}} \quad \text{(II.5.1)}$$

The output signal from each nerve is necessarily discrete in nature. Therefore it is possible to give explicit expresses for signal characteristics M_i and S_i^2. By definition M_i and S_i are given by

$$M_i = \frac{m_i \tau_i}{d_i}$$

(II.5.2) and

$$S_i^2 = \frac{s_i^2 \tau_i}{d_i} .$$

Using the formulations (II.3.32) and (II.3.33) for the mean m_i and the

incremental variance s_i^2 for a discrete input signal, M_i and S_i can be expressed as

$$(\text{II.5.3}) \qquad \left\{ \begin{aligned} M_i &= \sum_j \frac{c_{ij}}{d_i} \frac{\tau_i}{\tau_j} N_j \\ S_i^2 &= \sum_j \left(\frac{c_{ij}}{d_i} \right)^2 \frac{\tau_i}{\tau_j} N_j \end{aligned} \right.$$

where c_{ij} represents the modality and strength of the input received by nerve i from j, and the summation is taken over all nerves j in the net. Thus, the stationary activity of the network consisting of n nerves is given by the system

$$(\text{II.5.4}) \qquad N_i = e^{\{\sum_j \gamma_{ij} N_j - \delta_i\}} \quad ; \quad i = 1,2,\ldots,n$$

or equivalently

$$(\text{II.5.5}) \qquad \ell n \; N_i = \sum_j \gamma_{ij} N_j - \delta_i \; ; \quad i = 1,2,\ldots,n$$

where

$$(\text{II.5.6}) \qquad \left\{ \begin{aligned} &\gamma_{ij} = \left[\frac{\alpha_i c_{ij}}{d_i} + \beta_i \left(\frac{c_{ij}}{d_i} \right)^2 \right] \cdot \frac{\tau_i}{\tau_j} \quad \text{for} \quad i \neq j \\ &\text{and} \\ &\gamma_{ii} = \alpha_i \left(\frac{c_{ii}}{d_i} - 1 \right) + \beta_i \left(\frac{c_{ii}}{d_i} \right) . \end{aligned} \right.$$

The basic formulation (II.5.5) has been extended to include the effects of the refractory period, an external stimulus, and

to determine the dynamic behavior of the network. To account for the refractory period following an action potential, Johannesma multiplied the righthand side of (II.5.4) by

$$1 - p_i N_i \tag{II.5.7}$$

where p_i is the duration of the refractory period in unit of the membrane constant τ . The resulting stationary equations are

$$N_i = (1 - p_i N_i) e^{\{\sum_j \gamma_{ij} N_j - \delta_i\}} \qquad i = 1,2,3,\ldots,n \tag{II.5.7}$$

or equivalently

$$\ell n \frac{N_i}{1 - p_i N_i} = \sum_j \gamma_{ij} N_j - \delta_i \qquad i = 1,2,3,\ldots,n \tag{II.5.8}$$

Cowan (1972) has extended the treatment by considering the dynamic behavior of the network to be described by

$$\left(\frac{d}{dT} + 1\right) \ell n \frac{N_i}{1 - p_i N_i} = \sum_j \alpha_{ij} N_j - \delta_i ; \quad i = 1,2,..,n \tag{II.5.9}$$

where $T = \frac{t}{\tau}$. System (II.5.9) accounts for only the interaction of the nerves of the network. If, however, an external input to each neuron is incorporated, then (II.5.9) is transformed to

$$\left(\frac{d}{dT} + 1\right) n \left(\frac{x_i}{1 - x_i}\right) = \varepsilon_i + \frac{1}{\beta_i} \sum_j \alpha_{ij} x_j , \; i = 1,2,3,..,n \tag{II.5.10}$$

where $x_i = 1 - p_i N_i$ is defined to be the sensitivity of the nerve and

ε_i contains the external input as parametric excitation.

The description of the neural network by equation (II.5.10) has been derived by Cowan (1968) in a more heuristic manner. For this derivation the mean frequency of responses $N_i(t)$ was assumed to be given by the logistic function

$$N_i(t) = \left[p_i \left(1 + e^{\beta\left(\frac{i(t)}{i_{th}} - 1\right)} \right) \right]^{-1} \tag{II.5.11}$$

where

$$\beta = \left(1 - \frac{i_o}{i_{th}} \right)^{-1} \ell n \left(\frac{1 - pN_o}{pN_o} \right) \tag{II.5.12}$$

i_{th} is the current which drives the nerve at the 50% rate, i_o is the smallest current which will elicit an impulse and N_o is the corresponding firing rate. Using the model for a patch of dendritic membrane derived by Rall (1962), Cowan determined the mean current "build up" in the cell membrane of the nerve to be

$$\left\langle i(t) \right\rangle = \frac{c\sigma}{C_M} \sum_{j=1}^{n} \delta g_{ij} E_j N_j \left\langle e^{-\frac{t}{c\tau}} \right\rangle \tag{II.5.13}$$

where $\langle \ \rangle$ denotes a suitable time average, $E_j = - E_M$ the membrane voltage, C_M is the membrane capacitance, g_{ij} is the conductance change associated with the EPSP, and c and σ are constants. Taking the time-average of $\left\langle e^{-\frac{t}{c\tau}} \right\rangle$ to be $\frac{\alpha_i}{c\tau}$ where $0 \leq \alpha_i \leq 1$ reduces

(II.5.13) to

$$\langle i(t)\rangle = \frac{c\sigma\alpha_i}{C_M} \sum_{j=1}^{n} \delta g_{ij} E_j N_j(t) \ . \tag{II.5.14}$$

Hence by substitution of (II.5.14), (II.5.12) is transformed to

$$N_i(t) = \left[p(1 + e^{-\frac{\beta c\sigma\alpha_i}{C_M i_{th}}} \sum_{j=1}^{n} \delta g_{ij} E_j N_j(t) + \beta) \right]^{-1} \tag{II.5.15}$$

which determines $N_i(t)$, the firing rate of the i^{th} nerve as a function of $N_j(t)$ the firing rate of the j^{th} nerve. Simplifying the notation by defining

$$x_i = 1 - p_i N_i \tag{II.5.16}$$

and letting

$$\left\{ \begin{aligned} & \delta g_{ij} E_j = \alpha_{ij} \\ & \frac{\beta c\sigma\alpha_i}{C_M i_{th} p_i} = \frac{1}{\beta_i} \\ \text{and} \quad & \\ & \varepsilon_i = \beta - \frac{1}{\beta_i} \sum_{j=1}^{n} \alpha_{ij} \end{aligned} \right. \tag{II.5.17}$$

reduces (II.5.17) to

$$\ell n \frac{x_i(t)}{1 - x_i(t)} = \varepsilon_i + \frac{1}{\beta_i} \sum_{j=1}^{n} \alpha_{ij} x_j(t) \ . \tag{II.5.18}$$

The heuristic assumption that the dynamic behavior of the neural network is given by

$$(\text{II.5.19}) \qquad \left(\frac{d}{dT} + 1\right) \ell n \frac{x_i(t)}{1 - x_i(t} = \varepsilon_i + \frac{1}{\beta_i} \sum_{j=1}^{n} \alpha_{ij} x_j$$

completes the development of the neural equation.

Cowan (1968, 1972) also determined the properties of a specific case of (II.5.18) for which there is no self inhibition or excitation and for which the net is symmetrical. Mathematically, these criteria are given by

$$(\text{II.5.20}) \qquad \begin{gathered} \alpha_{ii} = 0 \\ \text{and} \\ \alpha_{ii} + \alpha_{ji} = 0 \quad . \end{gathered}$$

With these assumptions the hypothetical network resembles those present in the cerebral cortex and thalamus. For large external input, that is for large ε_i , (II.5.19) is closely approximated by

$$(\text{II.5.21}) \qquad \frac{dx_i}{dT} = (\varepsilon_i + \frac{1}{\beta_i} \sum_{j=1}^{n} \alpha_{ij} x_j) x_i (1 - x_i)$$

which is of a form closely related to the Lotka Volterra equations for predator-prey-interactions.

The properties of (II.5.21) can be studied using Gibbs statistical mechanics. To obtain applicable form for (II.5.20), the transformation

(II.5.22) $$v_i = \frac{\frac{x_i}{q_i}}{1 - x_i}$$

where q_i the stationary state of the network given by

(II.5.23) $$\varepsilon_i\beta_i + \sum_{j=1}^{n} \alpha_{ij}q_i = 0$$

is applied. Hence (II.5.21) is reduced to the equivalent form

(II.5.24) $$\frac{dv_i}{dT} = \sum_{j=1}^{n} \gamma_{ij} \frac{\partial G}{\partial v_j}$$

where

(II.5.25) $$\gamma_{ij} = \frac{\alpha_{ij}}{\beta_i\beta_j}$$

and where

(II.5.26) $$G = \sum_j \beta_j[\ell n \ (1 + q_j e^{v_j}] - q_j v_j$$

is the Liapunov function for the system. Since

(II.5.27) $$\frac{dG}{dT} = 0$$

then the activity of the net is asymptotically stable and oscillations about the stationary states gradually damp out.

Equation (II.5.22) can be extended to account for the fluctuations of the activity in the neuron by assuming

(II.5.28) $$\frac{dv_i}{dT} = \sum_{j=1}^{n} \gamma_{ij} \frac{\partial G}{\partial v_j} dT + dB(T)$$

where $dB(T)$ is a Langevin term with variance parameter k_i. The Fokker-Planck equation for the probability density-function $f(v_1,v_2,\ldots,v_{2n},T)$ associated with the Langevin equation (II.5.28) is given by

(II.5.29) $$\frac{\partial f}{\partial T} = \sum_{i=1}^{n} \left(\frac{}{\partial v_i} [\sum_{j=1}^{n} \gamma_{ij} \frac{\partial G}{\partial v_j} f] + \frac{k_i}{2} \frac{\partial^2 f}{\partial v_i^2} \right)$$

with equilibrium solution

(II.5.30) $$f(v_1,v_2,\ldots,v_{2n}) = e^{-\beta G} .$$

Furthermore, since G is a sum function for each individual variable, then

(II.5.31) $$f(v_i)dv_i = e^{-\beta G_i} dv_i .$$

This particular result justifies the treatment of the network as a Gibbs ensemble.

A number of results were obtained by Cowan (1970) using a Gibbs ensemble treatment. The equilibrium density was determined to be

(II.5.32) $$p(x_i)dx_i = \frac{x_i^{p-1}(1 - x_i)^{q-1}dx_i}{B(p,q)}$$

where $B(p,q)$ is the Euler β-function for which $p = \frac{\beta_i q_i}{\theta}$ and $q = \frac{\beta_i(1 - q_i)}{\theta}$ and θ measures the amplitude of the fluctuation of activity which is given by

$$\theta = \beta_i \frac{\frac{(x_i - q_i)^2}{x_i(1 - x_i)}}{1 - \frac{(x_i - q_i)^2}{x_i(1 - x_i)}} \quad . \tag{II.5.33}$$

Using the equilibrium diversity, it was possible to determine the interval density function, amplitude density function of membrane potential, and the mean rate at which fluctuation in activity occur. With these functions, it was possible to determine certain general conclusions regarding the net. In particular, it was found that the nerves of the network spend most of their time either completely off or else firing at their maximum rates.

§II.6 Improved Nerve Network Models

The model proposed in §II.5 for the activity of a nerve network forms the basis for a number of network models which have been considered. Each of these models extends the original model to incorporate certain physiological features of the nerve which are not inherent in the original. Mathematically these improvements are accomplished through modifications of the basic interaction equation (II.5.11). In §II.6 three improved nerve network models are considered.

The first modification of the model was made in order to account for self-inhibition in the nerves. By (II.5.10), the stationary activity of the net, consisting of n members, is determined by the system

$$(\text{II.6.1}) \qquad x_i = \frac{1}{1 + e^{-[\varepsilon_i + \frac{1}{\beta_i}\sum \alpha_{ij} x_j]}} \qquad \text{for} \quad i = 1,2,\dots,n$$

where x_i is the sensitivity of the i^{th} nerve, ε_i accounts for external stimulation, and α_{ij} given by (II.5.6), represents the influence of the j^{th} nerve on i^{th} nerve. To incorporate self-inhibition in the formulation, it was proposed that the dynamic behavior of the network is described by

$$(\tau\frac{d}{dt} + \gamma_i)x_i = \frac{1}{1 + e^{-[\varepsilon_i + \sum\alpha_{ij}x_j]}} \quad \text{for} \quad i = 1,2,\ldots,n$$

(II.6.2) where

$$\alpha_{ii} = 0 ,$$

the constant β_i in (II.6.1) is assumed to be equal to 1 , and γ_i is a nonnegative constant which represents the self-inhibition of the i^{th} nerve cell (Oguztoreli: 1972).

Oguztoreli (1972) has investigated the behavior of the solution of (II.6.2) for the case in which the initial conditions are given by

(II.6.3) $$x_i(0) = x_{i,o} \quad \text{where} \quad 0 < x_{i,o} < 1 \quad \text{for} \quad i = 1,2,3,\ldots$$

and the network model contains infinitely many elements. Using the contraction-mapping principle, Oguztoreli succeeded in proving there exists a unique solution of (II.6.2) in an interval $0 \leq t \leq h$, which is determined by initial condition (II.6.3). The domain of h was determined by the conditions for the required contraction map. It was also demonstrated that in the interval $0 \leq t \leq h$, $x_i(t)$ is monotonic. For small values of γ_i , weak self-inhibition, $x_i(t)$ is decreasing. Furthermore, the mean value of the sensitivities given by

(II.6.4) $$\overline{x_n}(t) = \frac{1}{n}\sum_{j=1}^{n} x_{i_j}(t)$$

is defined in $0 \leq t \leq h$, and $0 \leq \overline{x_n}(t) \leq 1$. Since $\overline{x_n}(t)$ is the

sum of monotonic functions then it is of bounded variation in $0 \leq t \leq h$ and therefore may exhibit random oscillations.

The steady state equations of system (II.6.2) given by

$$\text{(II.6.5)} \qquad \gamma_i x_i = \frac{1}{1 + e^{-[\varepsilon_i + \sum_{j=1}^{n} \alpha_{ij} x_j]}} \qquad \text{for } i = 1,2,3,\ldots$$

with initial condition (II.6.3) have also been analyzed. The existence of a unique solution has been demonstrated and was determined to be stable if the conditions

$$\text{(II.6.6)} \qquad \begin{aligned} &\sum_{j=1}^{\infty} |\alpha_{ij}| \leq 1 \\ &\text{and} \\ &0 < \gamma_i < 1 + e^{-[1+\|\varepsilon_i\|]} \\ &\text{for } i = 1,2,3,\ldots \end{aligned}$$

hold (Leung et al: 1972). By considering small perturbation of the steady state solutions it was possible to analyze the linear behavior of the solutions of (II.6.2) for small nerve networks consisting of one, two, and three elements. In each case, the conditions on the parameters were derived to determine when the solutions of (II.6.2) are stable or unstable and when they exhibit damped, periodic, or growing oscillatory behavior (Leung et al: 1972).

In the case of the actual nerve, with prolonged stimulation the firing rate declines and may terminate. This property of the nerve is known as adaptation and was previously discussed in §I.5 with regards to excitatory models. Stein (unpublished) suggested that the most appropriate manner to introduce adaptation into the interaction equation (II.6.2) is to add an integral term which is the convolution of an exponential with a factor proportional to the firing rate at a previous time. The resulting formulation for the activity of a network consisting of n nerves is

$$\text{(II.6.7)}\quad \tau\frac{dx_i}{dt} + \gamma_i x_i + \lambda_i \int_e^t e^{\frac{-\theta_i(t-\sigma)}{\tau}} x_i(\sigma)d\sigma = \frac{1}{1 + e^{-[\varepsilon_i + \sum_{j=1}^{n} \alpha_{ij}x_j]}}$$

$$\text{for}\quad i = 1,2,\ldots,n$$

where γ_i, λ_i and θ_i are constants for which γ_i and θ_i are positive. By defining

$$\text{(II.6.8)}\qquad x_{i,1} = \int_0^t e^{\frac{\theta_i(t-\sigma)}{\tau}} x_i(\sigma)d\sigma \quad \text{for}\quad i = 1,2,\ldots,n$$

then (II.6.7) is equivalent to the system of differential equations

$$\text{(II.6.9)}\quad \left\{\begin{aligned} \tau\frac{dx_i}{dt} &= -\gamma_i x_i - \lambda_i x_{i,1} + \frac{1}{1 + e^{-[\varepsilon_i + \sum_{j=1}^{n} \alpha_{ij}x_j]}} \\ \tau\frac{dx_{i,1}}{dt} &= -\theta_i x_{i,1} + \tau x_i \quad \text{for}\quad i = 1,2,\ldots,n\,. \end{aligned}\right.$$

The behavior of the system (II.6.7) has been analyzed with initial conditions

$$\text{(II.6.10)}\quad \begin{cases} x_i(0) = x_{i,o} \quad \text{where} \quad 0 < x_{i,o} < 1 \\ \text{and} \\ x_{i,1}(0) = 0 \end{cases}$$

for the cases in which $n = 1$ and $n = 2$.

For $n = 1$, (II.6.7) is

$$\text{(II.6.11)}\qquad \tau \frac{dx_1}{dt} + \gamma_1 x_1 + \lambda_1 \int_0^t e^{\frac{-\theta_1(t-\sigma)}{\tau}} x_1(\sigma)d\sigma = \frac{1}{1 + e^{-\varepsilon_1}}$$

or, by (II.6.9)

$$\text{(II.6.12)}\quad \begin{cases} \tau \dfrac{dx_1}{dt} = -\gamma_1 x_1 - \lambda_1 x_{1,1} + \dfrac{1}{1 + e^{-\varepsilon_1}} \\ \tau \dfrac{dx_{1,1}}{dt} = -\theta_1 x_{1,1} + \tau x_1 \end{cases}$$

with initial conditions

$$\text{(II.6.13)}\quad \begin{cases} x_1(0) = x_{1,0} \; ; \quad 0 < x_{1,0} < 1 \\ \text{and} \\ x_{1,1}(0) = 0 \; . \end{cases}$$

Let x_1^* and $x_{1,1}^*$ be the steady-state solutions of (II.6.12), that is, the solutions for

(II.6.14)
$$\left\{\begin{aligned} &\gamma_1 x_1 + \lambda_1 x_{1,1} = \frac{1}{1 + e^{-\varepsilon_1}} \\ &\tau x_1 - \theta_1 x_{1,1} = 0 \,. \end{aligned}\right.$$

Clearly, x_1^* and $x_{1,1}^*$ and unique solutions if and only if

(II.6.15)
$$-\gamma_1\theta_1 - \tau\lambda_1 \neq 0$$

holds. The necessary and sufficient condition in order that x_1^* remain bounded within the domain of definition (0,1) for the sensitivities, is determined by algebraic solution of (II.6.14), to be

(II.6.16)
$$\lambda_1 > -\frac{\gamma_1\theta_1}{\tau} + \frac{\theta_1}{(1 - e^{-\varepsilon_1})} \,.$$

In order to study the behavior of the solutions of system (II.6.12), it is assumed that

(II.6.17)
$$\begin{aligned} &x_1 = x_1^* + y_1 \quad \text{where} \quad y_1 = y_1(t) \\ &x_{1,1} = x_{1,1}^* + y_{1,1} \quad \text{where} \quad y_{1,1} = y_{1,1}(t) \end{aligned}$$

solve (II.6.12). Hence, by simple analysis,

(II.6.18)
$$\begin{aligned} &\tau \frac{dy_1}{dt} = \gamma_1 y_1 - \lambda_1 y_{1,1} \\ &\tau \frac{dy_{1,1}}{DT} + \tau y_1 - \theta_1 y_{1,1} \end{aligned}$$

and the corresponding characteristic equation is

$$\begin{vmatrix} -\frac{\gamma_1}{\tau} - s & \frac{\lambda_1}{\tau} \\ \frac{\tau}{\tau} & -\frac{\theta_1}{\tau} - s \end{vmatrix} = 0 \ . \tag{II.6.19}$$

Expanding (II.6.19) yields the equation of the form

$$b_o s^2 + b_1 s + b_2 = 0 \tag{II.6.20}$$

where

$$\begin{cases} b_1 = 1 \\ b_1 = \frac{1}{\tau}(\gamma_1 + \theta_1) \\ b_2 = \frac{1}{\tau}(\gamma_1\theta_1 + \lambda_1\tau) \ . \end{cases} \tag{II.6.21}$$

Furthermore, the determinants Δ_1 and Δ_2 defined by

$$\begin{cases} \Delta_1 = |b_1| \\ \text{and} \\ \Delta_2 = \begin{vmatrix} b_1 & b_o \\ 0 & b_2 \end{vmatrix} = b_1 b_2 \end{cases} \tag{II.6.22}$$

in the case of (II.6.21) are given by

$$\begin{cases} \Delta_1 = \frac{1}{\tau}(\gamma_1 + \theta_1) \\ \text{and} \\ \Delta_2 = \frac{1}{\tau^3}(\gamma_1 + \theta_1)(\gamma_1\theta_1 + \lambda_1\tau) \ . \end{cases} \tag{II.6.23}$$

By the Routh-Hurwitz criterion, the real part of the roots s of (II.6.20) are negative provided the coefficients b_o, b_1, and b_2 and the determinants Δ_1 and Δ_2 are positive. If the Routh-Hurwitz criterion is satisfied then solutions of (II.6.12) are stable, otherwise they are unstable. By the definition of the coefficients for system (II.6.7) and by (II.6.15), which insures the uniqueness of solution for (II.6.12), the Routh-Hurwitz criterion is satisfied in the case of (II.6.20). Hence solutions of (II.6.12) are stable. The discriminant of characteristic equation (II.6.20) is given by

$$D_1 = \frac{1}{\tau^2} (\gamma_1 + \theta)^2 - \frac{4}{\tau^2} (\gamma_1 \theta_1 + \lambda_1 \tau) . \tag{II.6.24}$$

The roots of (II.6.20) are real if $D_1 \geq 0$ and complex if $D_1 < 0$. Thus the solutions of (II.6.20) are stable and nonoscillatory if $D_1 \geq 0$, that is if

$$\lambda_1 \leq \frac{(\gamma_1 - \theta_1)^2}{4\tau} \tag{II.6.25}$$

and are stable and of damped oscillation if $D < 0$, in which case

$$\lambda_1 > \frac{(\gamma_1 - \theta_1)^2}{4\tau} . \tag{II.6.26}$$

Furthermore, since $b_1 \neq 0$ periodic solutions of (II.6.20) do not exist.

For $n = 2$, (II.6.7) is given by

$$\begin{cases} \tau \dfrac{dx_1}{dt} + \gamma_1 x_1 + \lambda_1 \displaystyle\int_0^t e^{\frac{-\theta_1(t-\sigma)}{\tau}} x_1(\sigma)d\sigma = \dfrac{1}{1 + e^{-[\varepsilon_1+\alpha_{12}x_2]}} \\ \\ \tau \dfrac{dx_2}{dt} + \gamma_2 x_2 + \lambda_2 \displaystyle\int_0^t e^{\frac{-\theta_2(t+\sigma)}{\tau}} x_2(\sigma)d\sigma = \dfrac{1}{1 + e^{-[\varepsilon_1+\alpha_{21}x_2]}} \end{cases} \tag{II.6.27}$$

or equivalently, by the system of differential equations

$$\begin{cases} \tau \dfrac{dx_1}{dt} = - \gamma_1 x_1 - \lambda_1 x_{1,1} + \dfrac{1}{1 + e^{-[\varepsilon_1 + {}_{12}x_2]}} \\ \\ \tau \dfrac{dx_2}{dt} = - \gamma_2 x_2 - \lambda_2 x_{2,1} + \dfrac{1}{1 + e^{-[\varepsilon_2 + {}_{21}x_1]}} \\ \\ \tau \dfrac{dx_{1,1}}{dt} = -\theta_1 x_{1,1} + \tau x_1 \\ \\ \tau \dfrac{dx_{2,1}}{dt} = -\theta_2 x_{2,1} + \tau x_2 \end{cases} \tag{II.6.28}$$

with initial condition

$$\begin{cases} x_i(0) = x_{i,o} \quad \text{where} \quad 0 < x_{i,o} < 1 \\ \text{and} \\ x_{i,1}(0) = 0 \quad \text{for} \quad i = 1,2 \;. \end{cases} \tag{II.6.29}$$

In order to examine the behavior of (II.6.28) it is first necessary to demonstrate the existence and uniqueness of the solutions of the steady state equations for system (II.6.28) given by

(II.6.30)
$$\left\{\begin{aligned} x_1 &= -\delta_1\lambda_1 x_{1,1} + \frac{\delta_1}{1 + e^{-\alpha_1-\beta_{12}x_2}} \\ x_2 &= -\delta_2\lambda_2 x_{2,1} + \frac{\delta_1}{1 + e^{-\alpha_2-\beta_{21}x_1}} \\ x_{1,1} &= \frac{\tau}{\theta_1} x_1 \\ x_{2,1} &= \frac{\tau}{\theta_2} x_2 \end{aligned}\right.$$

where $\delta_i = \frac{1}{\gamma_1}$ for $i = 1,2$. Let $x_{1,1} = x_3$ and $x_{2,1} = x_4$ and consider the Banach Space X of vector functions $x(t)$, which have continuous components $x_1(t), x_2(t), x_3(t), x_4(t)$ such that $0 \leq x_i(t) \leq 1$ for $i = 1,2$ and $t \geq 0$. Further assume that X is equipped with the norm

(II.6.31)
$$||x|| = \max_{i,t} |x_i(t)| \quad .$$

The boundary conditions, $0 \leq x_i(t) \leq 1$ for $i = 1,2$ and $t \geq 0$, result from the definition of the sensitivities.

To determine the existence and uniqueness of the solutions of (II.6.30) it is necessary to determine a contraction mapping T on X . Let T be the operator defined on X by

(II.6.32)
$$Tx = z$$

where z is the vector (z_1, z_2, z_3, z_4) and

$$z_1 = -\delta_1\lambda_1 x_3 + \frac{\delta_1}{1 + e^{-\varepsilon_1 - \alpha_{12}x_2}}$$

$$\text{(II.6.33)} \qquad \begin{cases} z_2 = -\delta_2\lambda_2 x_4 = \dfrac{\delta_2}{1 + e^{-\varepsilon_2 - \alpha_{21}x_1}} \\[2ex] z_3 = \dfrac{\tau}{\theta_1}\, x_1 \\[2ex] z_4 = \dfrac{\tau}{\theta_2}\, x_2 \, . \end{cases}$$

T will map X into X if it can be shown that $z(t)$ is continuous and that $0 \leq z_i(t) \leq 1$ for $i = 1,2$ and $t \geq 0$. By definition $z(t)$ is continuous for $t > 0$. To determine the boundary conditions it is necessary to consider two cases for each of the components z_1 and z_2 . Let $\lambda_1 \geq 0$ and consider

$$\text{(II.6.34)} \qquad z_1 = \delta_1\lambda_1 x_3 + \frac{\delta_1}{1 + e^{-\varepsilon_1 - \alpha_{12}x_2}} \quad .$$

Since the function

$$\text{(II.6.35)} \qquad f(\omega) = \frac{1}{1 + e^{-\omega}}$$

is monotonically increasing and

$$\text{(II.6.36)} \qquad -|\varepsilon_1| - |\beta_{12}| \leq \varepsilon_1 + \alpha_{12}x_2 \leq |\varepsilon_1| + |\alpha_{12}|$$

then

$$(\text{II.6.37}) \quad -\delta_1\lambda_1 + \frac{\delta_1}{1 + e^{|\varepsilon_1|+|\beta_{12}|}} \leq -\delta_1\lambda_1 x_3 + \frac{\delta_1}{1 + e^{-[\varepsilon_1+\alpha_{12}x_2]}} \leq$$

$$\leq \frac{\delta_1}{1 + e^{-|\varepsilon_1|-|\alpha_{12}|}} \;.$$

Hence for $\lambda_1 \geq 0$, $0 \leq z_1 \leq 1$ if

$$(\text{II.6.38}) \qquad \begin{cases} \dfrac{\delta_1}{1 + e^{-|\varepsilon_1|-|\alpha_{12}|}} \leq 1 \\ \text{and} \\ -\delta_1\lambda_1 + \dfrac{\delta_1}{1 + e^{|\varepsilon_1|+|\alpha_{12}|}} \geq 0 \end{cases}$$

that is, if

$$(\text{II.6.39}) \qquad \begin{cases} \gamma_1 \geq \dfrac{1}{1 + e^{-|\varepsilon_1|-|\alpha_{12}|}} \\ \text{and} \\ \lambda_1 \leq \dfrac{1}{1 + e^{|\varepsilon_1|+|\alpha_{12}|}} \end{cases} \;.$$

For $\lambda_1 < 0$ in (II.6.34)

$$(\text{II.6.40}) \qquad \frac{\delta_1}{1 + e^{|\varepsilon_1|+|\alpha_{12}|}} \leq -\delta_1\lambda_1 x_3 + \frac{\delta_1}{1 + e^{-\varepsilon_1-\alpha_{12}x_2}} \leq$$

$$\leq -\delta_1\lambda_1 + \frac{\delta_1}{1 + e^{-|\varepsilon_1|-|\alpha_{12}|}}$$

by (II.6.35) and (II.6.36). Hence $0 \leq z_1 \leq 1$ for $\lambda_1 < 0$ if

$$\text{(II.6.41)} \qquad \begin{array}{l} \alpha_1 \geq \dfrac{1}{1 + e^{-|\varepsilon_1| - |\alpha_{12}|}} \\ \text{and} \\ \lambda_1 \geq \dfrac{1}{1 + e^{-|\varepsilon_1| - |\alpha_{12}|}} - \gamma_1 \ . \end{array}$$

Combining conditions (II.6.39) and (II.6.41) reveals that $0 \leq z_1 \leq 1$ if

$$\text{(II.6.42)} \quad \left\{ \begin{array}{l} \alpha_1 \geq \dfrac{1}{1 + e^{-|\varepsilon_1| - |\alpha_{12}|}} \\ \text{and} \\ \dfrac{1}{1 + e^{-|\varepsilon_1| - |\alpha_{12}|}} - \alpha_1 \leq \lambda_1 \leq \dfrac{1}{1 + e^{|\varepsilon_1| + |\alpha_{12}|}} \ . \end{array} \right.$$

In a similar manner it can be shown that $0 \leq z_2 \leq 1$ if

$$\text{(II.6.43)} \quad \left\{ \begin{array}{l} \alpha_2 \geq \dfrac{1}{1 + e^{-|\varepsilon_2| - |\alpha_{21}|}} \\ \text{and} \\ \dfrac{1}{1 + e^{-|\varepsilon_2| - |\alpha_{21}|}} \leq \lambda_2 \leq \dfrac{1}{1 + e^{|\varepsilon_2| + |\alpha_{21}|}} \ . \end{array} \right.$$

Thus T maps X into X if (II.6.42) and (II.6.43) are satisfied. T is a contraction mapping on X if there exists a number ρ such that

$$\text{(II.6.44)} \qquad \begin{array}{l} 0 < \rho < 1 \\ \text{and} \\ \|Tx - T\tilde{x}\| = \rho \|x - \tilde{x}\| \end{array}$$

for all functions x and $\tilde{x}$ of $\mathcal{X}$. Consider $|z_1 - \tilde{z}_1|$.

$$|z_1 - \tilde{z}_1| = \left| -\delta_1\lambda_1 x_3 + \frac{\delta_1}{1 + e^{-\epsilon_1 - \alpha_{12}x_2}} + \delta_1\lambda_1 x_3 - \frac{\delta_1}{1 + e^{-\epsilon_1 - \alpha_{12}\tilde{x}_3}} \right|$$

$$\leq |\delta_1\lambda_1| \cdot |x_3 - \tilde{x}_3| + |\delta_1| \left| \frac{1}{1 + e^{-\epsilon_1 - \alpha_{12}x_2}} - \frac{1}{1 + e^{-\epsilon_1 - \alpha_{12}\tilde{x}_2}} \right| .$$

Hence by the mean value theorem of calculus

$$|z_1 - \tilde{z}_1| \leq |\delta_1\lambda_1||x_3 - \tilde{x}_3| + |\delta_1||-\alpha_{12}x_2 + \alpha_{12}\tilde{x}_2| \left| \frac{-e^{-\omega^*}}{\left(1 + e^{-\omega^*}\right)^2} \right|$$

where ω^* is a constant for which

$$-\varepsilon_1 - \alpha_{12}x_2 < \omega^* < -\epsilon_1 - \alpha_{12}\tilde{x}_2 .$$

By elementary calculus the function

$$f(\omega) = \frac{e^{-\omega}}{\left(1 + e^{-\omega}\right)^2} \tag{II.6.45}$$

attains its maximum value $\frac{1}{4}$ at $\omega = 0$. Therefore

$$\begin{aligned} |z_1 - \tilde{z}_1| &\leq |\delta_1\lambda_1||x_3 - \tilde{x}_3| + \frac{|\delta_1||\alpha_{12}|}{4} |x_2 - \tilde{x}_2| \\ &\leq |\delta_1\lambda_1| \|x - \tilde{x}\| + \frac{\delta_1\alpha_{12}}{4} \|x - \tilde{x}\| \\ &= \delta_1(|\lambda_1| + \frac{|\alpha_{12}|}{4}) \|x - \tilde{x}\| . \end{aligned} \tag{II.6.46}$$

Similarly

$$|z_2 - \tilde{z}_2| \leq \delta_2(|\lambda_2| + \frac{|\alpha_{21}|}{4})\|x - \tilde{x}\| . \tag{II.6.47}$$

For $|z_3 - \tilde{z}_3|$,

$$|z_3 - \tilde{z}_3| = |\frac{\tau}{\theta_1} x_1 - \frac{\tau}{\theta_1} \tilde{x}_1| \leq \frac{\tau}{\theta_1}\|x - \tilde{x}\| . \tag{II.6.48}$$

Similarly

$$|z_3 - \tilde{z}_3| \leq \frac{\tau}{\theta_2} \|x - \tilde{x}\| . \tag{II.6.49}$$

Thus T will be a contraction mapping on X if

$$\left\{ \begin{array}{l} \delta_1(|\lambda_1| + \frac{|\alpha_{12}|}{4} < 1 \\ \\ \delta_2(|\lambda_2| + \frac{|\alpha_{21}|}{4} < 1 \\ \\ \frac{\tau}{\theta_1} \\ \text{and} \\ \frac{\tau}{\theta_2} < 1 \end{array} \right. \tag{II.6.50}$$

that is, if

$$(\text{II}.6.51)\qquad \begin{cases} \gamma_1 > \dfrac{4|\lambda_1| + |\alpha_{12}|}{4} \\[2ex] \gamma_2 > \dfrac{4|\lambda_2| + |\alpha_{21}|}{4} \\[2ex] \theta_1 > \tau \\ \text{and} \\ \theta_1 > \tau \,. \end{cases}$$

If (II.6.51) is satisfied by the parameters of (II.6.30) then by the contraction mapping theorem there exists an unique x^* in X such that

$$(\text{II}.6.52)\qquad Tx^* = x^* \,.$$

Hence the components $x_1^*, x_2^*, x_3^* = x_{1,1}^*$ and $x_4^* = x_{2,1}$ of x^* form the unique solution set of (II.6.30).

To study the behavior of the solutions of (II.6.28), let

$$(\text{II}.6.53)\qquad \begin{cases} x_i = x_i^* + y_i \quad \text{where} \quad y_i = y_i(t) \\ \text{and} \\ x_{i,1} = x_{i,1}^* + y_{i,1} \quad \text{where} \quad y_{i,1} = y_{i,1}(t) \end{cases}$$

for $i = 1,2$. In this case, (II.6.30) is given by the system

$$\begin{cases} \tau \dfrac{dy_1}{dt} = -\gamma_1(x_1^* + y_1) - \lambda_1(x_{1,1}^* + y_{1,1}) + \dfrac{1}{1 + e^{-\varepsilon_1 - \alpha_{12}(x_2^* + y_2)}} \\[3ex] \tau \dfrac{dy_2}{dt} = -\gamma_2(x_2^* + y_2) - \lambda_2(x_{2,1}^* + y_{2,1}) + \dfrac{1}{1 + e^{-\varepsilon_2 - \alpha_{21}(x_1^* + y_1)}} \end{cases}$$

$$\text{(II.6.54)} \begin{cases} \tau \dfrac{dy_{1,1}}{dt} = -\theta_1(x^*_{1,1} + y_{1,1}) + \tau(x^*_1 + y_1) \\[2ex] \tau \dfrac{dy_{1,2}}{dt} = -\theta_2(x^*_{2,1} + y_{2,1}) + \tau(x^*_2 + y_2) \; . \end{cases}$$

System (II.6.54) can be linearized about the steady-state values by obtaining the Taylor Series expansion of the functions

$$\text{(II.6.55)} \begin{cases} g_1(y_1) = \dfrac{1}{1 + e^{-\varepsilon_1 - \alpha_{12}(x^*_2 + y_2)}} \\[3ex] g_2(y_2) = \dfrac{1}{1 + e^{-\varepsilon_2 - \alpha_{21}(x^*_1 + y_1)}} \; . \end{cases}$$

If y_1 and y_2 are chosen sufficiently small then the nonlinear terms of these expansions can be neglected and the linearized form for (II.6.54) will be

$$\text{(II.6.56)} \begin{cases} \tau \dfrac{dy_1}{dt} = -\gamma_1 y_1 - \lambda_1 y_{1,1} + \left[\dfrac{\alpha_{12} e^{-\varepsilon_1 - \alpha_{12} x^*_2}}{1 + e^{-\varepsilon_1 - \alpha_{12} x^*_2}} \right] y_2 \\[4ex] \tau \dfrac{dy_2}{dt} = -\gamma_2 y_2 - \lambda_2 y_{2,1} + \left[\dfrac{{}_{21} e^{-\varepsilon_2 - \alpha_{21} x^*_1}}{1 + e^{-\varepsilon_2 - \alpha_{21} x^*_1}} \right] y_1 \\[4ex] \tau \dfrac{dy_{1,1}}{dt} = -\theta_1 y_{1,1} + \tau y_1 \\[3ex] \tau \dfrac{dy_{1,2}}{dt} = -\theta_2 y_{2,1} + \tau y_2 \; . \end{cases}$$

By letting X_1 and X_2 denote the expressions

$$(II.6.57) \qquad \left\{ \begin{array}{l} \dfrac{e^{-\varepsilon_2 - \alpha_{21} x_1^*}}{1 + e^{-\varepsilon_2 - \alpha_{21} x_1^*}} \\ \text{and} \\ \dfrac{e^{-\varepsilon_1 - \alpha_{12} x_2^*}}{1 + e^{-\varepsilon_1 - \alpha_{12} x_2^*}} \end{array} \right.$$

respectively, then the characteristic equation for (II.6.56) is

$$(II.6.58) \qquad \begin{vmatrix} -\dfrac{\gamma_1}{\tau} - s & \dfrac{\alpha_{12}}{\tau} X_2 & -\dfrac{\lambda_1}{\tau} & 0 \\ \dfrac{\alpha_{21}}{\tau} X_1 & -\dfrac{\gamma_2}{\tau} - s & 0 & -\dfrac{\lambda_2}{\tau} \\ \dfrac{\tau}{\tau} & 0 & -\dfrac{\theta_1}{\tau} - s & 0 \\ 0 & \dfrac{\tau}{\tau} & 0 & -\dfrac{\theta_2}{\tau} - s \end{vmatrix} = 0 .$$

Equation (II.6.58) can be expanded to the fourth order equation

$$(II.6.59) \qquad b_o s^4 + b_1 s^3 + b_2 s^2 + b_3 s + b_4 = 0$$

where

$$\text{(II.6.60)}\quad \left\{ \begin{aligned} b_o &= 1 \\ b_1 &= \frac{1}{\tau}(\gamma_1 + \gamma_2 + \theta_1 + \theta_2) \\ b_2 &= \frac{1}{\tau^2}\{(\gamma_1+\gamma_2)(\theta_1+\theta_2) + \alpha_1\alpha_2 + \theta_1\theta_2 + \lambda_1\tau + \lambda_2\tau \\ &\qquad - \alpha_{12}\alpha_{21}X_1X_2\} \\ b_3 &= \frac{1}{\tau^3}\{\gamma_1\gamma_2(\theta_1+\theta_2) + \theta_1\theta_2(\gamma_1+\gamma_2) + \lambda_1\tau(\gamma_2 + \theta_2) \\ &\qquad + \lambda_2\tau(\gamma_1+\theta_1) - \alpha_{12}\alpha_{21}X_1X_2(\theta_1+\theta_2)\} \\ b_4 &= \frac{1}{\tau^4}\{\theta_1\theta_2\gamma_1\gamma_2 + \gamma_1\theta_1\lambda_2\tau + \gamma_2\theta_2\lambda_1\tau + \lambda_1\lambda_2\tau^2 \\ &\qquad - \theta_1\theta_2\alpha_{12}\alpha_{21}X_1X_2\} . \end{aligned} \right.$$

By evaluating the determinants

$$\Delta_1 = b_1$$

$$\text{(II.6.61)}\quad \left\{ \begin{aligned} \Delta_2 &= \begin{vmatrix} b_1 & b_o \\ b_3 & b_2 \end{vmatrix} \\ \Delta_3 &= \begin{vmatrix} b_1 & b_o & 0 \\ b_3 & b_2 & b_1 \\ 0 & b_4 & b_3 \end{vmatrix} \\ \Delta_4 &= \begin{vmatrix} b_1 & b_o & 0 & 0 \\ b_3 & b_2 & b_1 & 0 \\ 0 & b_4 & b_3 & b_2 \\ 0 & 0 & 0 & b_4 \end{vmatrix} \end{aligned} \right.$$

the Routh Hurwitz criterion can be applied to determined the stability of the solutions for (II.6.30) in terms of the parameters. By rewriting (II.6.59) as the product of two quadratic terms given by

$$(s^2 + a_1 s + a_2)(s^2 + a_3 s + a_4) \tag{II.6.62}$$

where

$$\left\{\begin{array}{l} b_1 = a_1 + a_3 \\ b_2 = a_2 + a_4 + a_1 a_3 \\ b_3 = a_1 a_4 + a_2 a_3 \\ b_4 = a_2 a_4 \end{array}\right.$$

it is possible, by examining the discriminant of each term, to determine whether the solutions of (II.6.59) are real or complex. Thus it is possible to determine the parameteric conditions for the existence and number of oscillatory solutions of (II.6.27). The oscillatory solutions are either damped or growing in nature. This results from the fact $b_1 > 0$ which eliminates the possibility of the existence of periodic solutions.

An interesting special case of (II.6.27) is that for which the two nerves have the same linear behavior to the same input. In terms of the formulation this is accomplished by assuming

$$\left\{\begin{array}{l} \gamma_1 = \gamma_2 = \gamma \\ \theta_1 = \theta_2 = \theta \\ \text{and} \\ \lambda_1 = \lambda_2 = \lambda \quad . \end{array}\right. \tag{II.6.63}$$

In this case characteristic equation (II.6.59) is reduced to

(II.6.64) $$(-\frac{\gamma}{\tau} - s)(-\frac{\theta}{\tau} - s) - \frac{\lambda}{\tau}^{2} - \frac{\alpha_{12}\alpha_{21}X_1X_2}{\tau^2}(-\frac{\theta}{\tau} - s)^2 = 0 .$$

If the two nerves are assumed to be mutually inhibitory or excitatory, that is

(II.6.65) $$\alpha_{12}\alpha_{21} > 0$$

then the solutions of (II.6.64) satisfy either

(II.6.66) $$(-\frac{\gamma}{\tau} - s)(-\frac{\theta}{\tau} - s) + \frac{\lambda}{\tau} = \sqrt{A}(-\frac{\theta}{\tau} - s)$$

or

(II.6.67) $$(-\frac{\gamma}{\tau} - s)(-\frac{\theta}{\tau} - s) + \frac{\lambda}{\tau} = -\sqrt{A}(-\frac{\theta}{\tau} - s)$$

where

(II.6.68) $$A = \frac{\alpha_{12}\alpha_{21}X_1X_2}{\tau^2} .$$

Hence the roots of (II.6.64) are

(II.6.69) $$s_{1,2} = \frac{1}{2}\frac{\gamma}{\tau} + \frac{\theta}{\tau} + \sqrt{A} \pm \sqrt{(-\frac{\gamma}{\tau} + \frac{\theta}{\tau} - \sqrt{A})^2 - \frac{4}{\tau}}$$

and

(II.6.70) $$s_{3,4} = -\frac{1}{2} \quad -(\frac{\gamma}{\tau} + \frac{\theta}{\tau}) + \sqrt{A} \pm \sqrt{(-\frac{\gamma}{\tau} + \frac{\theta}{\tau}\sqrt{A})^2 - \frac{4\lambda}{\tau}} .$$

Applying the Routh-Hurwitz criterion it can be shown that the solutions

of (II.6.21), which correspond to the roots s_1 and s_2 of (II.6.4) are stable if and only if

$$\left\{\begin{array}{l} \theta + \gamma + \theta\sqrt{A} > 0 \\ \text{and} \\ \gamma\theta + \lambda + \theta\sqrt{A} > 0 \quad . \end{array}\right. \tag{II.6.71}$$

Similarly the solutions corresponding to the roots s_3 and s_4 are stable if and only if

$$\left\{\begin{array}{l} \theta + \gamma - \theta\sqrt{A} > 0 \\ \text{and} \\ \gamma\theta + \lambda + \theta\sqrt{A} > 0 \; . \end{array}\right. \tag{II.6.72}$$

In order for oscillatory solutions to exist $\lambda > 0$ in both (II.6.69) and (II.6.70) and for s_1 and s_2

$$- \gamma + \theta + 2\sqrt{\lambda} > \sqrt{A} > - \gamma + \theta - 2\sqrt{x} \tag{II.6.73}$$

and for s_3 and s_4

$$- \gamma + \theta + 2\sqrt{\lambda} > \sqrt{4} > - \gamma + \theta - 2\sqrt{\lambda} \; . \tag{II.6.74}$$

Thus it is possible to determine for (II.6.27), for the case in which two identical nerves are mutually inhibitory or excitatory, the condition on the parameters in order for the solutions to be stable or unstable, and to be of nonoscillatory or of damped or growing oscillatory behavior. This particular special case has been solved by numerical means to determine its behavior (Stein et al: 1973).

The finally extension of the basic neural model has been

derived in order to include the physiological phenomena of self-excitation as well as self-inhibition. Both phenomena have been encorporated by adding convolution integrals to the basic formulation. The resulting interaction equation for a nerve network containing n elements is

(II.6.75)

$$\frac{1}{a_i}\frac{dx_{i1}}{dt} + x_{i1} =$$

$$= \frac{1}{1 + e^{[-\varepsilon_i - \sum_{j=1}^{n} \alpha_{ij} x_{j1} - b_i \int e^{-p_i(t-\sigma)} x_{i1} d\sigma + b_i \int e^{-q_i(t-\sigma)} x_{i1} d\sigma}}$$

for $i = 1,2,3,\ldots,n$.

The behavior of the model given by (II.6.75) has been analyzed for networks which include up to five elements (Stein et al: 1973).

SUMMARY

In the thesis two basic types of mathematical models for the activities of the nerve have been considered. Chapter I contains those models which account for the recorded electrical behavior of the nerve. Those in Chapter II are concerned with the impulse-processing behavior of the nerve.

In Chapter I a number of different models for excitation in the squid giant nerve axon were discussed. Each model was able to simulate to a degree certain aspects of the axon's behavior. It was demonstrated in §I.5 that it is possible to give a generalized formulation for excitation for which the previously discussed models are special case. The excitation models have also been extended. By assuming the axon possessed the properties of a core conducting cable the propagation of an action potential can be modelled. This results by combining a formulation for excitation with the cable equation. The Hodgkin-Huxley formulation for excitation in the squid nerve axon has been modified to model excitation and propagation in myelinated nerves which are structurally different from that of the squid nerve. Finally in Chapter I, two models were considered which demonstrated that the distance between the synapse and soma in electronic terms has considerable influence on the amplitude and time course of the membrane potentials recorded at the soma which result from synaptic activity.

In Chapter II, three models which attempt to account for neuronal variability have been discussed. As in the case of the excitation models for the squid nerve axon, it was possible to determine a general formulation for which these three models can be considered as special cases. By analysing the behavior of a special case of this general formulation, the Imperfect Integrator, an input-output relationship between the mean frequency of response for a nerve and the input signal characteristics has been determined. This relationship forms the basic interaction equation for a nerve network model. Three extensions of this basic nerve network model were considered, each one of which incorporates certain physiological phenomena of the nerve not in the original model. For one of these extensions, that which incorporates accommodation of the nerve in the formulation, the linear behavior of the solutions has been analyzed for networks containing one and two elements.

The review has been restricted to the analysis of the activities of only the single nerve. In the case of the nerve network model considered the activity was determined in terms of the activity of the individual members. A class of models which has not been considered are those of a nerve network for which the net is considered as a continuous medium (Beurle: 1956, Griffin: 1963, and Cowan: 1972). For these models the active fraction of nerves as a function of time and space is the characteristic variable. The drawback of these models is that there is no connection made between the activities of the individual nerves and gross activity of the network. The interaction

equation (II.5.10) derived hopefully represents the intermediary between the mathematical models of activity of single nerve cells and those of the activity of nerve networks which are considered as a continuous medium.

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